DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.

SUMMARY

This policy addresses the coverage of Xyrem (sodium oxybate) for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy when appropriate criteria are met. The intent of this drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies.

- Narcolepsy sleep disorder defined as recurrent irresistible attacks of daytime sleepiness, often in conjunction with triad of cataplexy, sleep paralysis, and hypnagogic hallucinations.

- Updated diagnostic criteria include:
  - The American Psychiatric Association (APA) Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), contains diagnostic criteria for sleep-wake disorders, including narcolepsy, designed for use by mental health and medical clinicians who are not experts in sleep medicine (May 2013)
  - The American Academy of Sleep Medicine (AASM) International Classification of Sleep Disorders, Third Edition (ICSD-3), contains diagnostic criteria for sleep disorders, including narcolepsy. The ICSD-3 features content changes from ICSD-2, including new nomenclature, classifications, diagnostic criteria, and recommendations (Feb 2014)
    - The AASM ICSD-3 reclassified narcolepsy into two types (narcolepsy type 1 and narcolepsy type 2)
    - Narcolepsy Type 1 (also referred to as: hypocretin deficiency syndrome, narcolepsy-cataplexy, narcolepsy with cataplexy
    - Narcolepsy Type 2 (also referred to as: narcolepsy without cataplexy)

- There is no cure for narcolepsy. Overall goals of narcolepsy treatment include improving the safety of the patient as well as managing symptoms. Current pharmacotherapies focus on alleviating EDS or, when present, cataplexy, or both.

- Pharmacologic treatment of narcolepsy
  - The available pharmacologic therapies include medications that have been approved for the treatment of specific symptoms of narcolepsy, as well as several that are not approved but are used off-label because of their recognized utility in managing symptoms.
Of the FDA-approved drugs for narcolepsy, methylphenidate, amphetamines, and modafinil/armodafinil are approved only for EDS.

Sodium oxybate is approved for both EDS and cataplexy in adults. Sodium oxybate is often well tolerated and does improve the quality of life of narcoleptic patients. However, sodium oxybate has abuse potential due to its anxiolytic, hypnotic and euphoric effects, and has possible neurotoxic side effects.

Off-label drugs include antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs), all of which are recommended for cataplexy and to a lesser extent for hypnagogic hallucinations and sleep paralysis, albeit with a lower level of recommendation than approved drugs, and hypnotics as an option for disturbed nighttime sleep.

- The rationale for using antidepressants is that these medications strongly suppress rapid-eye-movement (REM) sleep, and cataplexy is probably the occurrence of REM sleep paralysis during wakefulness. Antidepressants mainly suppress cataplexy by increasing levels of norepinephrine and serotonin in the brain.
- As there have been no large clinical studies examining the effects of these medications on cataplexy, guidelines on their use are mainly based on the clinical experience of narcolepsy specialists. (Morgenthaler, AASM 2007)

Xyrem (sodium oxybate) oral solution is a C-III scheduled drug indicated for the treatment of cataplexy in narcolepsy, and is indicated for the treatment of excessive daytime sleepiness (EDS) in narcolepsy. Per the package insert, Xyrem may only be dispensed to patients enrolled in the Xyrem REMS Program.

There is a lack of comparative efficacy and safety data for sodium oxybate versus the other agents that have been used in treatment of narcolepsy and cataplexy, such as methylphenidate, dexamphetamine, modafinil, or armodafinil, in relieving the symptoms of cataplexy associated with narcolepsy or EDS associated with narcolepsy.

CLASSIFICATION: Central Nervous System Depressant

<table>
<thead>
<tr>
<th>FDA INDICATIONS</th>
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<tr>
<td>Excessive daytime sleepiness/cataplexy: Treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.a</td>
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<tr>
<td>- Cataplexy and narcolepsy</td>
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<td>- Narcolepsy, to treat excessive daytime sleepiness</td>
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Orphan drug designation: Treatment of narcolepsy and the auxiliary symptoms of cataplexy, sleep paralysis, hypnagogic hallucinations, and automatic behavior

Schedule III controlled substance for medical use. Schedule I controlled substance for illicit use (has been used as "date rape" drug. The active ingredient, sodium oxybate or gamma-hydroxybutyrate (GHB), is listed in the most restrictive schedule of the Controlled Substances Act (Schedule I). Thus, non-medical uses of Xyrem are classified under Schedule I.

Available as: Oral solution, 0.5 g per mL

Approved by the FDA:
July 2002: For the treatment of cataplexy attacks in patients with narcolepsy
November 2005: Indication expanded to include the treatment of excessive daytime sleepiness in patients with narcolepsy

Restricted access: Because of the risks of CNS depression, abuse, and misuse, sodium oxybate is available only through a restricted distribution program called the Xyrem REMS Program, using a centralized pharmacy. Prescribers and patients must enroll in the program.
Black Box Warnings

- Black Box Warning: Respiratory depression may occur; increased risk with compromised respiratory function
- Black Box Warning: Concurrent use with other CNS depressants; increased risk of respiratory depression, hypotension, profound sedation, syncope, and death; consider dose reduction, interruption, or discontinuation of one or more CNS depressants, including sodium oxybate
- Black Box Warning: Abuse or misuse has been reported and linked to serious CNS effects, including seizure, respiratory depression, decreased consciousness, coma, and death; monitoring of patients at risk recommended

**RECOMMENDATIONS/Coverage Criteria**

Xyrem (sodium oxybate) may be authorized for members who meet **ALL** of the following criteria [**ALL**]

1. **Prescriber specialty [**ALL**]**
   - Prescribed by, or in consultation with, a board-certified Sleep Medicine Specialist, neurologist, pulmonologist, or psychiatrist. Submit consultation notes if applicable.
   - **NOTE:** Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.
   - Prescriber is registered with the Xyrem REMS Program
     - **Prescriber Requirements:** Prescribers must enroll in the Xyrem REMS Program and must agree to abide by the rules of the Xyrem REMS Program including patient screening, counseling, patient enrollment in the Xyrem REMS Program, and patient monitoring.

2. **Diagnosis/Indication [**ALL**]**
   - Diagnostic criteria for **narcolepsy** confirmed by overnight polysomnography (PSG) followed by **multiple sleep latency test (MSLT)**. Documentation of testing results and provider interpretation for the PSG and MSLT [**ALL**]
     - Daily excessive daytime sleepiness for at least 3 months (AASM ICSD-3 Criteria)
     - Nocturnal polysomnography (PSG) confirmation*
       - *Overnight polysomnography to rule out other conditions and confirm adequate sleep before first Multiple Sleep Latency Test (MSLT)*
     - Positive MSLT* including: [**ALL**]
       - Mean Sleep Latency ≤ 8 minutes
       - 2 or more sleep onset rapid eye movement (REM) periods < 15 minutes

   **EXCEPTION** to positive MSLT test for Type 1 Narcolepsy (cataplexy in narcolepsy): Hypocretin-1 ≤ 110 pg/mL (or < 1/3 of mean normal control values) may be alternative to MSLT sleep study

   **Note:**
   - The diagnosis of narcolepsy is established on the basis of characteristic clinical features combined with nocturnal PSG and a MSLT.
   - MSLT is sleep study monitoring 4-5 nap periods each 2 hours apart with a minimum of 6 hours of sleep required the night before testing
   - Appendix 1: Quantifying Sleepiness
Diagnosis of EITHER Type 1 or Type 2 narcolepsy and ALL condition specific criteria are met: [A OR B]

A. Type 1 Narcolepsy (cataplexy in narcolepsy) [ALL]
   ☑ Member has cataplexy defined as more than one episode of generally brief (less than 2 minutes) usually bilaterally symmetrical, sudden loss of muscle tone with retained consciousness
   ☑ EXCEPTION to positive MSLT test: Hypocretin-1 ≤ 110 pg/mL (or < 1/3 of mean normal control values) may be alternative to MSLT for diagnosis of narcolepsy with cataplexy
   Reference: European Federation of Neurological Societies (EFNS) guidelines on disease-specific CSF investigations can be found in Eur J Neurol 2009 Jun;16(6):760

B. Type 2 Narcolepsy [narcolepsy without cataplexy; excessive daytime sleepiness (EDS) in narcolepsy] [ALL]
   ☑ Other conditions that cause EDS have been ruled out or treated, including (but not limited to):
     o shift work
     o the effects of substances or medications or their withdrawal
     o sleep phase disorder
     o effects of sedating medications
     o idiopathic hypersomnolence
     o insufficient sleep at night (sleep deprivation)
     o obstructive sleep apnea, central sleep apnea
     o periodic limb movement disorder (including restless legs syndrome)
     o depression
     o Circadian rhythm disorders (including delayed sleep phase syndrome)
     o sedating medications

3. Age/Gender/Other restrictions [ONE]
   ☑ 16 years of age or older
     ➢ The FDA has not established the safety and efficacy of sodium oxybate for use in neonates, infants, children and adolescents with narcolepsy who are < 16 years of age. Sodium oxybate may affect endocrine function with chronic use, including growth hormone secretion. The effects on a child in whom growth and development are incomplete are uncertain.

   ☐ Member does not have ANY of the following contraindications to therapy: [ANY]
     ☑ Concomitant treatment with a sedative hypnotic agent
     ☑ Succinic semialdehyde dehydrogenase deficiency (i.e. an inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia)
4. Step/Conservative Therapy/Other condition Requirements [ALL]

- Xyrem (sodium oxybate) therapy is not prescribed with, nor will be administered concomitantly with, ANY of the following drugs within the past 90 days: [ANY]
  - Sedative hypnotic agents (e.g., benzodiazepines, barbiturates, zolpidem)
  - Other CNS depressants
  - Alcohol
  - Provigil (modafinil) or Nuvigil (armodafanil):

  EXCEPTIONS: Case-by-case review with Pharmacy/Medical Director.
  ➢ Refer to Appendix 3 for considerations of combination therapy of modafinil (Provigil) and sodium oxybate Xyrem

MOLINA REVIEWER: Verify pharmacy claims data for applicable drugs above within the last 90 days, OR for new members to Molina Healthcare, confirm applicable drugs in medical chart history

- Type 1 Narcolepsy (cataplexy in narcolepsy)
Member did not achieve treatment goals or experienced inadequate clinical response after an adherent trial at maximum therapeutic dose, persistent intolerable adverse effects or contraindication to at least ONE (1) medication from BOTH of the following: [BOTH: 1 AND 2]

1) Non-amphetamine stimulant OR Amphetamine-based stimulant or a methylphenidate-based stimulant [ONE]

  - Non-amphetamine stimulant: modafanil (Provigil) or armodafanil (Nuvigil)

  NOTE: Authorization may be required per Plan/State formulary. Molina Reviewer may facilitate prior authorization if member meets criteria for Provigil or Nuvigil by entering authorization if member meets criteria or request additional information from Prescriber.

  - Amphetamine-based products: amphetamine/dextroamphetamine mixed salts; amphetamine/dextroamphetamine mixed salts extended-release; dextroamphetamine extended-release
  - OR
  - Methylphenidate-based products: methylphenidate, methylphenidate extended-release, dexmethylphenidate

  AND

2) Tricyclic Antidepressants (TCA) OR Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin-norepinephrine Reuptake Inhibitor (SNRI) [ONE]

  - TCA: imipramine, nortriptyline, protriptyline, clomipramine, etc.

  - SSRI/SNRI: fluoxetine, venlafaxine, atomoxetine, etc.
Type 2 Narcolepsy [narcolepsy without cataplexy]

Member did not achieve treatment goals or experienced inadequate clinical response after an adherent trial at maximum therapeutic dose, persistent intolerable adverse effects or contraindication to at least ONE (1) medication from BOTH of the following: [1 AND 2]

1) Non-amphetamine stimulant [ONE]
   - modafanil (Provigil)
   - armodafanil (Nuvigil)

   NOTE: Authorization may be required per Plan/State formulary. Molina Reviewer may facilitate prior authorization if member meets criteria for Provigil or Nuvigil by entering authorization if member meets criteria or request additional information from Prescriber.

   AND

2) Amphetamine-based stimulant OR methylphenidate-based stimulant [ONE]
   - Amphetamine-Based Products: amphetamine/dextroamphetamine mixed salts; amphetamine/dextroamphetamine mixed salts extended-release; dextroamphetamine extended-release
   - Methylphenidate based products: methylphenidate, methylphenidate extended-release, dexmethylphenidate

5. Contraindications/Exclusions to Xyrem (sodium oxybate) therapy [ANY]

Authorization will not be granted if ANY of the following conditions apply [ANY]

- Non-FDA approved indications
- Hypersensitivity to Xyrem (sodium oxybate) or any ingredient in the formulation
- Co-administration with CNS depressant anxiolytics, sedatives, and hypnotics or other sedative CNS depressant drugs
  - Administration with alcohol or other psychoactive drugs can potentiate the effects of sodium oxybate.
- Co-administration with alcohol (ethanol)
  - Ethanol is contraindicated in patients using sodium oxybate. The combined use of alcohol (ethanol) with sodium oxybate may result in potentiation of the CNS-depressant effects of sodium oxybate and alcohol.
- Succinic Semialdehyde Dehydrogenase Deficiency
  - This rare disorder is an in-born error of metabolism and variably characterized by mental retardation, hypotonia, and ataxia.

Exclusions [ANY]

- History of drug abuse
  - Sodium oxybate is a CNS depressant with potential for misdirection and abuse and patients should be evaluated for a history of drug abuse.
- Uncontrolled hypertension (due to sodium content)
6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member’s medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.
CONTINUATION OF THERAPY

Xyrem (sodium oxybate) may be authorized for continuation of therapy if meet ALL of the following criteria are met: [ALL]

1. Initial Coverage Criteria

- Member currently meets ALL initial coverage criteria
- Member is evaluated by the prescribing physician no less frequently than every 6 months
- Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually

2. Compliance

- Adherence to therapy at least 85% of the time as verified by Prescriber and member’s medication fill history (review Rx history for compliance), including:
  - Adherent to the prescribed medication regimen
  - Tolerance to therapy
  - No severe adverse reactions or drug toxicity

  NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

  NOTE: History of non-compliance or non-adherence as verified by member’s medication fill history or prescription drug profile may result in continuation of therapy request not being authorized. [MOLINA MEDICAL/pharmacy reviewer to verify]

- Member is not being treated with any sedative hypnotic agents (e.g., benzodiazepines, barbiturates, zolpidem)
  MOLINA REVIEWER: Verify by paid claims history

- Member is not consuming any alcohol concomitantly with sodium oxybate

- Dose requested for continuation of therapy does not exceed 9 gm/day (18 mL/day or 540 mL per 30 days)

  NOTE: The efficacy and safety at doses higher than 9 grams per night have not been established, and doses greater than 9 grams per night generally should not be administered. Therefore, requests for higher doses will not be authorized.

3. Labs/Reports/Documentation required [ALL APPLICABLE]

Documentation of efficacy and positive response to Xyrem (sodium oxybate) therapy as evidenced by response of decreasing cataplexy events and improvement in score for appropriate test (e.g. Epworth Sleepiness Scale, Clinical Global Impression of Change, etc.) for EDS [ALL APPLICABLE]

- Decrease or reduction in the frequency of cataplexy events/attacks associated with Xyrem therapy

- Decrease or reduction in symptoms of excessive daytime sleepiness associated with Xyrem therapy

- For excessive daytime sleepiness (EDS): Improvement in the Epworth Sleepiness Scale (ESS), Clinical Global Impression of Change or Maintenance of Wakefulness Test (MWT)
  - Refer to Appendix 1: Quantifying Sleepiness’ for additional information on ESS
4. **Discontinuation of Treatment [ANY]**

Discontinue treatment if ANY of the following conditions applies: [ANY]
- Intolerable adverse effects or drug toxicity
- Persistent and uncorrectable problems with adherence to treatment
- Poor response to treatment as evidenced by physical findings and/or clinical symptoms

**Contraindications/Exclusions to Xyrem (sodium oxybate) therapy [ANY]**

Authorization will not be granted if ANY of the following conditions apply [ANY]
- Non-FDA approved indications
- Hypersensitivity to Xyrem (sodium oxybate) or any ingredient in the formulation\(^{a,b}\)
- Co-administration with CNS depressant anxiolytics, sedatives, and hypnotics or other sedative CNS depressant drugs
  - Administration with alcohol or other psychoactive drugs can potentiate the effects of sodium oxybate.
- Co-administration with alcohol (ethanol)
  - Ethanol is contraindicated in patients using sodium oxybate. The combined use of alcohol (ethanol) with sodium oxybate may result in potentiation of the CNS-depressant effects of sodium oxybate and alcohol. Therefore, patients should be warned strongly against the use of any alcoholic beverages in conjunction with sodium oxybate.
- Succinic Semialdehyde Dehydrogenase Deficiency
  - This rare disorder is an in-born error of metabolism and variably characterized by mental retardation, hypotonia, and ataxia.

**Exclusions [ANY]**

- History of drug abuse
  - Sodium oxybate is a CNS depressant with potential for misdirection and abuse and patients should be evaluated for a history of drug abuse.
- Uncontrolled hypertension (due to sodium content)
1. Recommended Dosage [ALL]

- Recommended Starting Dose: 4.5 g/day, divided into two equal doses of 2.25 g. Xyrem is required to be taken at bedtime while in bed and again 2.5 to 4 hours later.

  - **Cataplexy and narcolepsy**
    - Initial: 2.25 g orally at bedtime and 2.25 g taken 2.5 to 4 hours later (total initial dose 4.5 g/night); increase dose by 1.5 g/night (0.75 g/dose) at weekly intervals; take while in bed and lie down immediately
    - Maintenance: 6 to 9 g orally per night administered in 2 equally divided doses at bedtime and 2.5 to 4 hours later; take while in bed and lie down immediately; maximum dose: 9 g/night

  - **Narcolepsy, to treat excessive daytime sleepiness**
    - Initial, 2.25 g orally at bedtime and 2.25 g taken 2.5 to 4 hours later (total initial dose 4.5 g/night); increase dose by 1.5 g/night (0.75 g/dose) at weekly intervals; take while in bed and lie down immediately
    - Maintenance: 6 g to 9 g orally per night administered in 2 equally divided doses at bedtime and 2.5 to 4 hours later; take while in bed and lie down immediately; maximum dose: 9 g/night

- Usual Effective Dose: 6 to 9 g/day

- Maximum Dose: 9 g/day, divided into two equal doses

  **NOTE:** The efficacy and safety at doses higher than 9 grams per night have not been established, and doses greater than 9 grams per night generally should not be administered. Therefore, requests for higher doses will not be authorized.

2. Authorization Limit [ALL]

- Quantity limit: 9 grams per day; 18 mL per day OR 540 mL per 30 days

- Dispensing limit: limited to 1 month

- Duration of initial authorization: 3 months

- Duration of continuation of treatment: up to 6 months at a time

3. Route of Administration [ALL]

- Xyrem (sodium oxybate) is considered a **self-administered** medication. The Food and Drug Administration has deemed the drug(s) or biological product(s) in this MCP to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

- If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.
This policy addresses the coverage of Xyrem (sodium oxybate) for the treatment of adult patients with **excessive daytime sleepiness and cataplexy in patients with narcolepsy** when appropriate criteria are met.

All other uses of Xyrem (sodium oxybate) that are not an FDA-approved indication or not included in the ‘Coverage Criteria’ section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

*Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.

*FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.

### Summary of Evidence/Position Statements

**Narcolepsy** is defined as a sleep disorder defined as recurrent irresistible attacks of daytime sleepiness, often in conjunction with triad of cataplexy, sleep paralysis, and hypnagogic hallucinations

- Cataplexy is sudden reduction or loss of muscle tone, triggered by strong emotions, while maintaining consciousness (Zeman A et al.; Naumann A et al; Billiard M et al.)
- Hypnagogic hallucinations are vivid hallucinations at sleep initiation or at awakening
- Sleep paralysis is inability to move when falling asleep or awakening, often frightening
- REM sleep is phase of sleep characterized by rapid eye movement, loss of muscle tone which repeats in cycles during night, associated with experience of dreaming

- Updated diagnostic criteria include the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) and International Classification of Sleep Disorders Third Edition (ICSD-3).
  - The American Psychiatric Association (APA) *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), contains diagnostic criteria for sleep-wake disorders, including narcolepsy, designed for use by mental health and medical clinicians who are not experts in sleep medicine (May 2013)
  - The American Academy of Sleep Medicine (AASM) *International Classification of Sleep Disorders, Third Edition* (ICSD-3), contains diagnostic criteria for sleep disorders, including narcolepsy. The ICSD-3 features content changes from ICSD-2, including new nomenclature, classifications, diagnostic criteria, and recommendations (Feb 2014).
    - The AASM ICSD-3 reclassified narcolepsy into two types (narcolepsy type 1 and narcolepsy type 2)
    - Narcolepsy Type 1 (also referred to as: hypocretin deficiency syndrome, narcolepsy-cataplexy, narcolepsy with cataplexy)
    - Narcolepsy Type 2 (also referred to as: narcolepsy without cataplexy)

- Hayes
  At the time of this writing, a Hayes Directory report or Hayes Rating is not available addressing Xyrem (sodium oxybate) in the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.

**Sodium Oxybate**

- Sodium salt of gamma hydroxybutyric acid (GHB), a naturally-occurring central nervous system transmitter with sedative and anesthetic properties. GHB has been used illegally as a drug of abuse and has been implicated as a date-rape drug as a date-rape drug.
- Common street names for GHB include Liquid Ecstasy, Liquid X, Liquid E, Salty Water, Organic Qualualude, and Grievous Bodily Harm.
Sodium oxybate (Xyrem) is classified as a Schedule III controlled substance by Federal law. The active ingredient, sodium oxybate or gamma-hydroxybutyrate (GHB), is listed in the most restrictive schedule of the Controlled Substances Act (Schedule I). Thus, non-medical uses of Xyrem are classified under Schedule I.

A CNS depressant: The precise mechanism of action of sodium oxybate in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of GHB, an endogenous compound and metabolite of the neurotransmitter gamma-aminobutyric acid (GABA). It is hypothesized that the therapeutic effects of sodium oxybate on cataplexy and excessive daytime sleepiness are mediated through GABA_B actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.

Safety
- Sodium oxybate carries boxed warnings for respiratory depression, CNS adverse adverse reactions (e.g. seizure, decreased consciousness, coma and death), and risk for substance abuse. For these reasons, sodium oxybate is classified as a Schedule III controlled substance and is subject to Xyrem REMs program. The REMs program restricts distribution to one pharmacy and requires ALL physicians and patients are registered with the program.
- The most common adverse reactions associated with sodium oxybate include nausea, dizziness, vomiting, somnolence, enuresis, and tremor. Sodium oxybate is contraindicated in patients currently taking sedative hypnotic agents or alcohol and in patients with succinic semialdehyde dehydrogenase deficiency.

Cataplexy and narcolepsy: FDA Labeled Indication

Efficacy

- **Trials N1 and N2.** The effectiveness of sodium oxybate in the treatment of cataplexy was established in two 4 week, randomized, double-blind, placebo-controlled trials in patients with narcolepsy (Trials N1 and N2). Patients were randomized to receive placebo or sodium oxybate dosed at 3 grams to 9 grams nightly. The primary efficacy endpoint for both of the trials was frequency of cataplexy attacks. **Both trials found that dose of 6 grams to 9 grams resulted in statistically significant reduction in frequency of cataplexy attacks.** The trials also found that discontinuation of sodium oxybate in patient who had been treated with it long term resulted in a significant increase in cataplexy attacks.

- In a 12-month, open-label extension study (N=118) following 4 weeks of treatment with sodium oxybate 3, 4.5, 6, 7.5, or 9 g nightly, cataplexy attacks/week continued to significantly decrease by an average of 24 attacks at 1 month and by an average of 35 attacks at 12 months. Overall improvement in daytime sleepiness was maximal after 2 months and significant at all doses, with an approximately 30% decrease in Epworth Sleepiness Scale from the pretreatment mean. That response was maintained throughout the study
  

- **Sodium Oxybate for Narcolepsy with Cataplexy: Systematic review and Meta-analysis**
  In a systematic review and meta-analysis of 5 short-term, randomized trials (study durations, 4 to 12 weeks) in 463 patients with narcolepsy and cataplexy and 278 patients with unknown cataplexy status, sodium oxybate 9 g/night significantly eliminated excessive daytime sleepiness compared with placebo, with significantly increased sleep latency (mean difference of 5.18 evaluated with the maintenance of wakefulness test in 2 studies in 192 patients), significantly decreased sleep attacks by 9.65 attacks/week (2 studies in 203 patients), and significantly increased the proportion of patients with a Clinical Global Impression of severity and Change (CGI) score of very much improved by 142% (3 studies in 280 patients). Sodium oxybate 4.5 g/night significantly decreased the cataplexy attacks by 8.5 attacks/week (2 studies in 124 patients). There was no significant between-group difference in the percentage of REM sleep before and after treatment (2 studies in 44 patients) and all studies excluded patients with sleep-disordered breathing (Alshaikh 2012) Using a different measure of effect, sodium oxybate alone (n=50) or when combined with modafinil (n=54) significantly decreased the Epworth Sleepiness Scale scores at week 5 (12 and 11 vs 16). The incidence of adverse events was greater with sodium oxybate plus modafinil (Black J, Houghton WC).
  
Efficacy

- Other agents that may be used for treatment of EDS include stimulants (e.g., modafinil, amphetamine, methamphetamine, methylphenidate, dextroamphetamine). These agents have shown benefit for treatment of EDS however, they are typically ineffective for cataplexy.

- Sodium oxybate
  The effectiveness of sodium oxybate in the treatment of EDS in narcolepsy was established in two 8 week, randomized, double-blind, placebo-controlled trials in patients with narcolepsy (Prescribing Information, January 2017). Patients were randomized to one of four groups:
  - placebo,
  - sodium oxybate 4.5 grams per night,
  - sodium oxybate 6 grams per night, or
  - sodium oxybate 9 grams per night
  The primary efficacy was extent of sleepiness in everyday situations [determined using Epworth Sleepiness Scale (ESS)] and change in symptoms of EDS (evaluated using Clinical Global Impression of Change tool). Sodium oxybate was associated with statistically significant differences with regard to both of the primary outcomes when compared to placebo.

- Sodium oxybate exhibited superior outcomes compared with placebo in 2 randomized, double-blind trials for the treatment of excessive daytime sleepiness in narcolepsy.

  ◆ Trial N3. The first trial evaluated patients (n=228) with moderate to severe symptoms, a median ESS (ESS; range 0 to 24) of 18 and Maintenance of Wakefulness Test (MWT) score of 8.25 minutes. Patients were randomized into 1 of 4 groups to receive either sodium oxybate 4.5 g/night; sodium oxybate 6 g/night; sodium oxybate 9 g/night; or placebo for a period of 8 weeks. While antidepressants were withdrawn during the study, stimulants were continued at stable doses. The primary outcomes were measured using the ESS and the Clinical Global Impression of Change (CGI-C) and patients were assessed based on the severity of narcolepsy at baseline. Patients being treated with 6 g/night (n=58) and 9 g/night (n=47) doses of sodium oxybate displayed statistically significant improvements on the ESS (-2 and -5 points, respectively, compared with -0.5 point with placebo; p less than 0.001) and on the CGI-C (52% and 64% responders, respectively, compared with 22% responders with placebo; p less than 0.001).

  ◆ Trial N4. The second trial evaluated patients (n=222) with moderate to severe symptoms of narcolepsy, a median ESS score of 15 and MWT score of 10.25 minutes. Additionally, prior to randomization, patients had to be taking modafinil for greater than or equal to 1 month at stable doses of 200, 400, or 600 mg daily.
  - Patients were randomized into 1 of 4 groups to receive for a period of 8 weeks:
    - sodium oxybate
    - Modafinil
    - sodium oxybate plus modafinil, or
    - placebo
  - Sodium oxybate was given as 6 g nightly for 4 weeks, increasing to 9g nightly for the other 4 weeks. Following the switch from modafinil to placebo, the mean average daytime sleep latency on the MWT decreased from 9.74 minutes at baseline to 6.87 minutes after 8 weeks (p<0.001).
  - In the sodium oxybate group, there was no decrease in sleep latency; authors suggest this shows that sodium oxybate is as efficacious as the previously administered modafinil.
  - The sodium oxybate/modafinil group showed an increase in daytime sleep latency from 10.43 minutes to 13.15 minutes (p<0.001), suggesting that the combination of drugs produces an additive effect. 2 The sodium oxybate group showed a decrease in median average ESS scores from 15 to 12; the sodium oxybate/modafinil group decreased from 15 to 11 (for both p<0.001). The Clinical Global Impression Change scale showed similar results.
Xyrem product information states that this trial was not designed to compare the effects of sodium oxybate and modafinil because patients on modafinil were not titrated to a maximally effective dose. The combination group reported a greater number of adverse effects than the other groups.

**CLINICAL PRACTICE GUIDELINES**

American Academy of Sleep Medicine (AASM 2007)
A 2007 practice report from the AASM states modafinil as the standard for treatment of daytime sleepiness due to narcolepsy; amphetamine, methamphetamine, dextroamphetamine and methylphenidate are also listed as effective treatments for EDS due to narcolepsy.

These guidelines stated that sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy, and is a standard treatment for cataplexy. The guideline also stated that sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis, but this is listed as an “option,” meaning that this represents a more uncertain clinical use, based on inconclusive or conflicting evidence or conflicting expert opinion.

"Standard" Recommendations
The report classifies the following as "standard" recommendations because they are generally accepted patient-care strategies that reflect a high degree of certainty:

- It is important to establish an accurate diagnosis of a specific hypersonomnia of central origin and evaluate other possible causes of excessive daytime sleepiness.
- Treatment objectives should include control of sleepiness and other sleep-related symptoms when present.
- Modafinil is effective for the treatment of daytime sleepiness from narcolepsy (unchanged from the previous recommendation and supported by 14 additional studies).
- Sodium oxybate is effective for the treatment of cataplexy, daytime sleepiness, and disrupted sleep from narcolepsy.
- Regular follow-up of patients with hypersonmia of central origin is necessary to monitor response to treatment, to respond to potential adverse effects of medications, and to enhance patients' adaptation to the disorder.

"Guideline" Recommendations
The following are classed as "guideline" recommendations because they reflect a moderate degree of clinical certainty:

- Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness from narcolepsy (unchanged from previous recommendations; these generic medications have a long history of use, but limited high-level evidence).
- Scheduled naps can be beneficial to combat sleepiness but seldom suffice as primary therapy for narcolepsy (unchanged).
- Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and reboxetine may be effective for cataplexy (expanded medication recommendation).
- Modafinil may be effective for the treatment of daytime sleepiness from multiple sclerosis (new recommendation based on 2 studies).

"Option" Recommendations
The following are classed as "option" recommendations because they reflect inconclusive or conflicting evidence, or conflicting expert opinion:

- Sodium oxalate, tricyclic antidepressants, SSRIs, and venlafaxine may be effective for hypnagogic hallucinations and sleep paralysis.
- Selegiline may be an effective treatment of cataplexy and daytime sleepiness.
- Ritanserin may be an effective treatment of daytime sleepiness from narcolepsy.
- Modafinil may be effective for treatment of daytime sleepiness from idiopathic hypersonmia and Parkinson's disease.
- Modafinil or methylphenidate may be effective treatment options for daytime sleepiness from myotonic dystrophy.
**Definitions**

**Cataplexy:** a condition, often associated with narcolepsy; marked by abrupt attacks of muscular weakness and hypotonia triggered by an emotional stimulus, such as mirth, anger, or fear.

**Excessive Daytime Sleepiness (EDS):** EDS refers to a condition where an individual person feels very drowsy during the day, even after getting adequate night time rest, and has a tendency to fall asleep or requires extra effort to avoid sleeping in inappropriate situations, such as at work or driving. This condition is also defined as a score greater than or equal to 10 on the Epworth Sleepiness Scale.

**Multiple Sleep Latency Test (MSLT):** This is a test used in conjunction with polysomnography (PSG) to determine the presence and severity of sleepiness. During this test, the subject is given the opportunity to take naps at specified time intervals. The test consists of four or five nap opportunities at two hour intervals. Each nap opportunity is 20 minutes in duration. Individuals with excessive daytime sleepiness may fall asleep almost immediately, while those without excessive sleepiness may not fall asleep at all. Severe sleepiness is usually associated with an MSLT mean sleep latency of less than 5 minutes. The presence of sleep onset rapid eye movement (REM) and the number of naps in which sleep REM occurs are also determined.

**Narcolepsy:** recurrent, uncontrollable, brief episodes of sleep often associated with hallucinations just beforehand or just afterward.

**Type 1 Narcolepsy:** narcolepsy with cataplexy in which patients have very low CSF hypocretin/orexin levels resulting from extensive loss of hypothalamic neurons

**Type 2 Narcolepsy:** narcolepsy without cataplexy in which patients have normal or mildly decrease CSF hypocretin/orexin level.

**Appendix**

**Appendix 1: Quantifying Sleepiness**

**Sleep studies**
- Overnight polysomnography to rule out other conditions and confirm adequate sleep before first Multiple Sleep Latency Test (MSLT)
- MSLT involves 4-5 nap periods, each 2 hours apart, with sleep study monitoring
- Maintenance of Wakefulness Test (MWT) is recording of time before falling asleep with patient semirecumbent in darkened room during four 20-minute trials separated by 2-hour intervals

**Epworth Sleepiness Scale (ESS)** may be used for diagnosis or monitoring
- patient rated level of daytime sleepiness
  - 0 = never dozes
  - 1 = slight chance of dozing
  - 2 = moderate chance of dozing
  - 3 = high chance of dozing
- 0-3 score applied to 8 normal situations
  - sitting and reading
  - watching television
  - sitting inactive in public place
  - passenger in car for an hour without break
  - lying down to rest in afternoon
  - sitting and talking to someone
• sitting quietly after lunch
• in car, stopped in traffic
  • score range 0-24
  • scores > 11 associated with high probability of sleep disorder

References:


APPENDIX 2: Sedative-Hypnotic Drug Information
Sedative-hypnotic drug products are a class of drugs used to induce and/or maintain sleep.
NOTE: The following list is not all inclusive. Check drug compendia for additional information.

Prescription Insomnia Drugs
• Ambien, Ambien CR (zolpidem tartrate)
• Butisol sodium (butabarbitral sodium)
• Carbralital (pentobarbital and carbromal)
• Dalmane (flurazepam hydrochloride)
• Doral (quazepam)
• Edluar (zolpidem tartrate)
• Halcion (triazolam)
• Intermezzo (zolpidem)
• Lunesta (eszopiclone)
• Placidyl (ethchlorvynol)
• Prosom (estazolam)
• Restoril (temazepam)
• Rozerem (ramelteon)
• Seconal (secobarbital sodium)
• Silenor (doxepin hydrochloride)
• Sonata (zaleplon)
• Zolpimist (zolpidem tartrate)

Over-the-counter (OTC) Insomnia Drugs
• Benadryl (diphenhydramine)*
• Unisom (doxylamine)*
*Also in many cold and headache combination products
APPENDIX 3: Combination of modafinil (Provigil) and sodium oxybate Xyrem

There is no high-quality evidence that combining sodium oxybate with modafinil substantially reduces drowsiness over either agent alone; however the following are points of considerations of combination therapy of modafinil (Provigil) and sodium oxybate Xyrem on a case-by-case basis:

- Trial N4 was a multicenter randomized, double-blind, placebo-controlled, parallel-group trial that evaluated 222 patients with moderate to severe symptoms at entry into the study including a median Epworth Sleepiness Scale score of 15, and a Maintenance of Wakefulness Test (see below) score of 10.3 minutes. At entry, patients had to be taking modafinil at stable doses of 200 mg, 400 mg, or 600 mg daily for at least 1 month prior to randomization. The patients enrolled in the study were randomized to one of 4 treatment groups: placebo, Xyrem, modafinil, or Xyrem plus modafinil. Xyrem was administered in a dose of 6 g per night for 4 weeks, followed by 9 g per night for 4 weeks. Modafinil was continued in the modafinil alone and the Xyrem plus modafinil treatment groups at the patient’s prior dose. Trial N4 was not designed to compare the effects of Xyrem to modafinil because patients receiving modafinil were not titrated to a maximal dose. Patients randomized to placebo or to Xyrem treatment were withdrawn from their stable dose of modafinil. Patients taking antidepressants could continue these medications at stable doses.

The primary efficacy measure in Trial N4 was the Maintenance of Wakefulness Test. The Maintenance of Wakefulness Test measures latency to sleep onset (in minutes) averaged over 4 sessions at 2-hour intervals following nocturnal polysomnography. For each test session, the subject was asked to remain awake without using extraordinary measures. Each test session is terminated after 20 minutes if no sleep occurs, or after 10 minutes, if sleep occurs. The overall score is the mean sleep latency for the 4 sessions.

In Trial N4, a statistically significant improvement in the change in the Maintenance of Wakefulness Test score from baseline at Week 8 was seen in the Xyrem and Xyrem plus modafinil groups compared to the placebo group. However, this trial was not designed to compare the effects of Xyrem to modafinil, because patients receiving modafinil were not titrated to a maximally effective dose.

- Guidelines from the European Federation of Neurological Societies (EFNS, 2006) recommend the following:
  - First line pharmacological treatment of EDS should rely on modafinil. Second line pharmacological treatment is methylphenidate. Sodium oxybate is a potential agent for first line therapy in the treatment of excessive daytime sleepiness of narcolepsy. The guidelines note that this is an increasingly common practice in the U.S. and is based on grade A evidence. In severe cases the combination of modafinil and sodium oxybate appears to be beneficial.
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**REFERENCES**

**Package Insert, FDA, Drug Compendia**


**Clinical Trials, Definitions, Peer-Reviewed Publications**


GOVERNMENT AGENCIES, PROFESSIONAL SOCIETIES, AND OTHER AUTHORITATIVE PUBLICATIONS


