Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for sodium oxybate when it is determined to be medically necessary because the following criteria have been met.

When Policy Topic is covered
Sodium oxybate may be considered medically necessary in patients with documented* narcolepsy when:

- The patient’s diagnosis is cataplexy (a sudden loss in muscle tone and deep tendon reflexes).
- OR

- The patient’s diagnosis is excessive daytime sleepiness and Provigil® in doses up to 400 mg daily and at least one other formulary treatment such as methylphenidate or dextroamphetamine have been ineffective, not tolerated, or contraindicated.

* A polysomnogram and multiple sleep latency test (MSLT) is provided as documentation to support the diagnosis.

Xyrem may only be dispensed to patients enrolled in the Xyrem REMS Program.

When Policy Topic is not covered
Sodium oxybate is considered investigational for other conditions or applications, including, but not limited to, the treatment of:

- Alcohol dependence and withdrawal,
- Fibromyalgia,
- Opioid dependence and withdrawal,
- Parkinsonism,
- Night eating syndrome,
- Myoclonus and essential tremor.

Considerations
XYREM REMS PROGRAM

High-Level Overview
Because of the risks of CNS depression, abuse, and misuse, XYREM is available only through a restricted distribution program called the XYREM REMS Program using the central pharmacy that is specially certified. Prescribers and patients must enroll in the program.

The XYREM REMS Program is designed to ensure that prescribers and patients are educated on and understand the risks and safe use conditions of XYREM and agree to follow the requirements of the XYREM REMS Program. The program also ensures that XYREM is dispensed from the specially certified central pharmacy.
Program Components

XYREM will be prescribed only by prescribers who are enrolled in the XYREM REMS Program.

XYREM will be dispensed and shipped only to patients who are enrolled in the XYREM REMS Program with documentation of safe use conditions.

XYREM will be dispensed only by the specially certified central pharmacy.

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Hayes Medical Technology Directory, Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

Description of Procedure or Service

Sodium oxybate (Xyrem®) is a medication used to reduce the number of cataplexy attacks and to reduce excessive daytime sleepiness in patients with narcolepsy. Sodium oxybate is a schedule III controlled substance.

Rationale

Sodium oxybate showed a statistically significant reduction in the weekly cataplexy attacks after 4 weeks of treatment, by about 6 to 12 attacks per week, compared to patients receiving placebo. (1-4, 14) Patients with excessive daytime sleepiness randomized to sodium oxybate showed a statistically significant but modest improvement in scores on rating scales to assess sleepiness and maintenance of daytime wakefulness compared to patients taking placebo after 8 weeks of treatment. (1,16,17) Approximately 80% of patients maintained concomitant stimulant use. There is weak evidence to support use of sodium oxybate in the treatment of conditions other than cataplexy in narcolepsy. (5-13,15,18,19)

Off-Label Uses

ALCOHOL DEPENDENCE AND WITHDRAWAL
- Two small randomized controlled trials have reported reduction of symptoms related to alcohol withdrawal compared to placebo or to clomethiazole. (7,9) Three small randomized controlled trials examined the use of sodium oxybate on alcohol craving, alcohol consumption and/or abstinence. While suggestive of a useful effect, more studies are needed to fully understand the role of sodium oxybate for the management of alcohol abuse. (8, 18-19)

FIBROMYALGIA

Scharf et al. studied 24 women meeting the American College of Rheumatology (ACR) criteria for fibromyalgia. Subjects received sodium oxybate 6 g/day or placebo for one month each in a double-blind, randomized, placebo-controlled crossover fashion. [6] After one month of each treatment, the mean “tender point index” (TPI) was reduced from baseline by 8.5 for sodium oxybate vs. an increase of 0.7 for placebo. While suggestive of an effect, the small size and high rate of patient non-completion in this trial (4/24 or 17%) render it not useful for recommending treatment. Larger, well-designed randomized controlled trials are needed.

OTHER INDICATIONS

Sodium oxybate has been studied in small, preliminary trials for possible efficacy in opiate withdrawal syndrome, parkinsonism, essential tremor, alcohol dependency and night-eating syndrome. Further research is needed to establish the clinical safety and efficacy of sodium oxybate for these indications. [10-13, 15, 19]

Safety

Contraindications to the use of sodium oxybate include: [1]
- Concomitant treatment with sedative hypnotic agents.
Use in patients with succinic semialdehyde dehydrogenase deficiency. This rare disorder is an
inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.

**Black-Box Warning [1]**

- Sodium oxybate should not be used with alcohol or other central nervous system (CNS)
depressants. It is the same chemical as gamma hydroxybutyrate (GHB), a known drug of
abuse. Abuse has been associated with some important CNS adverse events (including death).
Even at recommended doses, use has been associated with confusion, depression and other
neuropsychiatric events. Reports of respiratory depression occurred in clinical trials. Almost all
of the patients who received sodium oxybate during clinical trials were receiving CNS
stimulants.
- Important CNS adverse events associated with abuse of GHB include seizure, respiratory
depression and profound decreases in level of consciousness, with instances of coma and
death. For events that occurred outside of clinical trials, in people taking GHB for recreational
purposes, the circumstances surrounding the events are often unclear (e.g., dose of GHB taken,
the nature and amount of alcohol or any concomitant drugs).

- Sodium oxybate is available through the Xyrem Success Program, using a centralized
pharmacy 1-866-XYREM88® (1-866-997-3688). The Success Program provides educational
materials to the prescriber and the patient explaining the risks and proper use of sodium
oxybate, and the required prescription form. Once it is documented that the patient has read
and/or understood the materials, the drug will be shipped to the patient. The Xyrem Success
Program also recommends patient follow-up every 3 months. Physicians are expected to report
all serious adverse events to the manufacturer.

**References:**
2. U.S. Xyrem Multicenter Study Group 1: Sodium oxybate demonstrates long-term efficacy
3. Anonymous. A 12-month, open-label, multicenter extension trial of orally administered
4. Anonymous. A randomized, double blind, placebo-controlled multicenter trial comparing the
   effects of three doses of orally administered sodium oxybate with placebo for the treatment
5. Fuller DE, Hornfeldt CS From club drug to orphan drug: sodium oxybate (Xyrem) for the
6. Scharf MB, Baumann M, Berkowitz DV. The effects of sodium oxybate on clinical
   of gamma-hydroxybutyrate and clomethiazole in the treatment of alcohol withdrawal.
8. Gallimberti L, Ferri M, Ferrara SD, Fadda F, Gessa GL. Gamma-Hydroxybutyric acid in the
10. Rosen MI, Pearsall HR, Woods SW, Kosten TR. Effects of gamma-hydroxybutyric acid

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dru093.4 Page 7 of 8
    Muscarinic cholinergic mediation of the GH response to gamma-hydroxybutyric acid:
17. Weaver TE, Cuellar N. A randomized trial evaluating the effectiveness of sodium oxybate therapy on quality of life in narcolepsy. Sleep. 2006 Sep 1;29(9):1189-94.

**Billing Coding/Physician Documentation Information**

NA Xyrem is a pharmacy benefit

**Additional Policy Key Words**

5.01.531

**Policy Implementation/Update Information**

03/2009 New policy
04/2010 Reviewed – no changes made.
04/2011 Reviewed – no changes made.
04/2012 Reviewed – no changes made
04/2014 Reviewed – no changes made
04/2015 Reviewed – no changes made
04/2016 Reviewed – no changes to policy statement. Added REMS program info.

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