

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SODIUM OXYBATE ORAL SOLUTION safely and effectively. See full prescribing information for SODIUM OXYBATE ORAL SOLUTION. SODIUM OXYBATE oral solution, CIII
Initial U.S. Approval: 2002

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and MISUSE AND ABUSE

See full prescribing information for complete boxed warning.

- Respiratory depression can occur with sodium oxybate use (5.4).
- Sodium Oxybate Oral Solution is a Schedule III controlled substance and is the sodium salt of gamma hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma and death (5.2, 9.2).
- Because of the risks of CNS depression, abuse, and misuse, sodium oxybate is available only through the Sodium Oxybate REMS Program. Prescribers and patients must enroll in the program (5.3).

----- **RECENT MAJOR CHANGES** -----

Boxed Warning, Sodium Oxybate REMS Program 04/2015
Indications and Usage, Sodium Oxybate REMS Program (1) 04/2015
Dosage and Administration, Dose Adjustment with Co-administration of Divalproex Sodium (2.4) 04/2014
Warnings and Precautions, Sodium Oxybate REMS Program required components (5.3) 04/2015

----- **INDICATIONS AND USAGE** -----

Sodium Oxybate Oral Solution is a central nervous system depressant indicated for the treatment of:

- Cataplexy in narcolepsy (1.1).
- Excessive daytime sleepiness (EDS) in narcolepsy (1.2).

Sodium Oxybate Oral Solution may only be dispensed to patients enrolled in the Sodium Oxybate REMS Program (1).

----- **DOSAGE AND ADMINISTRATION** -----

- Initiate dose at 4.5 grams (g) per night administered orally in two equal, divided doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later (2.1).
- Titrate to effect in increments of 1.5 g per night at weekly intervals (0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) (2.1).
- Recommended dose range: 6 g to 9 g per night orally (2.1).

Total Nightly Dose	Take at Bedtime	Take 2.5 to 4 Hours Later
4.5 g per night	2.25 g	2.25 g
6 g per night	3 g	3 g
7.5 g per night	3.75 g	3.75 g

9 g per night	4.5 g	4.5 g
<ul style="list-style-type: none"> • Take each dose while in bed and lie down after dosing (2.2). • Allow 2 hours after eating before dosing (2.2). • Prepare both doses prior to bedtime; dilute each dose with approximately 1/4 cup of water in the provided dosing cups (2.2). • Patients with Hepatic Impairment: Starting dose is 2.25 g per night administered orally in two equal, divided doses of approximately 1.13 g at bedtime and approximately 1.13 g taken 2.5 to 4 hours later (2.3). • Concomitant use with divalproex sodium: an initial reduction in sodium oxybate dose of at least 20% is recommended (2.4, 7.2). 		

----- **DOSAGE FORMS AND STRENGTHS** -----

Oral solution, 0.5 g per mL (3)

----- **CONTRAINDICATIONS** -----

- Succinic semialdehyde dehydrogenase deficiency (4).
- In combination with sedative hypnotics or alcohol (4).

----- **WARNINGS AND PRECAUTIONS** -----

- CNS depression: Use caution when considering the concurrent use of sodium oxybate with other CNS depressants (5.1).
- Caution patients against hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after first initiating treatment until certain that sodium oxybate does not affect them adversely (5.1).
- Depression and suicidality: Monitor patients for emergent or increased depression and suicidality (5.5).
- Confusion/anxiety: Monitor for impaired motor/cognitive function (5.6).
- Parasomnias: Evaluate episodes of sleepwalking (5.7).
- High sodium content in sodium oxybate: Monitor patients with heart failure, hypertension, or impaired renal function (5.8).

----- **ADVERSE REACTIONS** -----

Most common adverse reactions (≥5% and at least twice the incidence with placebo) were nausea, dizziness, vomiting, somnolence, enuresis, and tremor (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact West-Ward Pharmaceuticals Corp. at 1-800-962-8364 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **USE IN SPECIFIC POPULATIONS** -----

- Pregnancy: Based on animal data, may cause fetal harm (8.1).
- Geriatric patients: Monitor for impaired motor and/or cognitive function when taking sodium oxybate (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 07/2016

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CENTRAL NERVOUS SYSTEM (CNS) DEPRESSION and MISUSE AND ABUSE

Sodium oxybate is a CNS depressant. In clinical trials at recommended doses obtundation and clinically significant respiratory depression occurred in sodium oxybate-treated patients. Almost all of the patients who received sodium oxybate during clinical trials in narcolepsy were receiving central nervous system stimulants [see *Warnings and Precautions (5.1)*].

Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB). Abuse of 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 [see *Warnings and Precautions (5.2)*].

Because of the risks of CNS depression, abuse, and misuse, sodium oxybate is available only through the Sodium Oxybate REMS Program using certified pharmacies. Prescribers and patients must enroll in the program. For further information call 1-800-XXX-XXXX [see *Warnings and Precautions (5.3)*].

1 INDICATIONS AND USAGE

Limitations of Use

Sodium Oxybate Oral Solution may only be dispensed to patients enrolled in the Sodium Oxybate REMS Program [see *Warnings and Precautions (5.3)*].

1.1 Cataplexy in Narcolepsy

Sodium Oxybate Oral Solution is indicated for the treatment of cataplexy in narcolepsy.

1.2 Excessive Daytime Sleepiness in Narcolepsy

Sodium Oxybate Oral Solution is indicated for the treatment of excessive daytime sleepiness (EDS) in narcolepsy.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe sodium oxybate must enroll in the Sodium Oxybate REMS Program and must comply with the requirements to ensure safe use of sodium oxybate [see *Warnings and Precautions (5.3)*].

2.1 Dosing Information

The recommended starting dose is 4.5 grams (g) per night administered orally in two equal, divided doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later (see Table 1). Increase the dose by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dose range of 6 g to 9 g per night orally. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

Table 1: Sodium Oxybate Dose Regimen (g = grams)

If A Patient's Total Nightly Dose is:	Take at Bedtime:	Take 2.5 to 4 Hours Later:
4.5 g per night	2.25 g	2.25 g
6 g per night	3 g	3 g
7.5 g per night	3.75 g	3.75 g
9 g per night	4.5 g	4.5 g

2.2 Important Administration Instructions

Take the first dose of sodium oxybate at least 2 hours after eating because food significantly reduces the bioavailability of sodium oxybate.

Prepare both doses of sodium oxybate prior to bedtime. Prior to ingestion, each dose of sodium oxybate should be diluted with approximately $\frac{1}{4}$ cup (approximately 60 mL) of water in the empty dosing cups provided with your prescription. Patients should take both doses of sodium oxybate while in bed and lie down immediately after dosing as sodium oxybate may cause them to fall asleep abruptly without first feeling drowsy. Patients will often fall asleep within 5 minutes of taking sodium oxybate, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night. Patients should remain in bed following ingestion of the first and second doses, and should not take the second dose until 2.5 to 4 hours after the first dose. Patients may need to set an alarm to awaken for the second dose. Rarely, patients may take up to 2 hours to fall asleep.

2.3 Dose Modification in Patients with Hepatic Impairment

The recommended starting dose in patients with hepatic impairment is 2.25 g per night administered orally in two equal, divided doses: approximately 1.13 g at bedtime and approximately 1.13 g taken 2.5 to 4 hours later [see *Use in Specific Populations* (8.6); *Clinical Pharmacology* (12.3)].

2.4 Dose Adjustment with Co-Administration of Divalproex Sodium

Pharmacokinetic and pharmacodynamic interactions have been observed when sodium oxybate is co-administered with divalproex sodium. For patients already stabilized on sodium oxybate, it is recommended that addition of divalproex sodium should be accompanied by an initial reduction in the nightly dose of sodium oxybate by at least 20%. For patients already taking divalproex sodium, it is recommended that prescribers use a lower starting sodium oxybate dose when introducing sodium oxybate oral solution. Prescribers should monitor patient response and adjust dose accordingly [see *Drug Interactions* (7.2) and *Clinical Pharmacology* (12.3)].

3 DOSAGE FORMS AND STRENGTHS

Sodium Oxybate Oral Solution is a clear to slightly opalescent oral solution, in a concentration of 0.5 g per mL.

4 CONTRAINDICATIONS

Sodium Oxybate Oral Solution is contraindicated in patients being treated with sedative hypnotic agents.

Patients should not drink alcohol when using Sodium Oxybate Oral Solution.

Sodium Oxybate Oral Solution is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency. This is a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.

5 WARNINGS AND PRECAUTIONS

5.1 Central Nervous System Depression

Sodium oxybate is a central nervous system (CNS) depressant. Alcohol and sedative hypnotics are contraindicated in patients who are using sodium oxybate. The concurrent use of sodium oxybate with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death. If use of these CNS depressants in combination with sodium oxybate is required, dose reduction or discontinuation of one or more CNS depressants (including sodium oxybate) should be considered. In addition, if short-term use of an opioid (e.g. post- or perioperative) is required, interruption of treatment with sodium oxybate should be considered.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that sodium oxybate does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking the second nightly dose of sodium oxybate. Patients should be queried about CNS depression-related events upon initiation of sodium oxybate therapy and periodically thereafter [*see Warnings and Precautions (5.3)*].

5.2 Abuse and Misuse

Sodium Oxybate Oral Solution is a Schedule III controlled substance. The active ingredient of Sodium Oxybate Oral Solution, sodium oxybate or gamma-hydroxybutyrate (GHB), is a Schedule I controlled substance. Abuse 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. The rapid onset of sedation, coupled with the amnesic features of sodium oxybate, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim). Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g. increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy) [*see Warnings and Precautions (5.3); Drug Abuse and Dependence (9.2)*].

5.3 Sodium Oxybate REMS Program

Because of the risks of central nervous system depression and abuse/misuse, sodium oxybate is available only through the Sodium Oxybate REMS Program.

Required components of the Sodium Oxybate REMS Program are:

- Use of certified pharmacies.
- Healthcare providers who prescribe sodium oxybate must complete the enrollment forms and comply with the requirements.
- Pharmacists, wholesalers and distributors must complete the enrollment forms and comply with the requirements.
- To receive Sodium Oxybate Oral Solution, patients must understand the risks and benefits of sodium oxybate.

Further information is available by calling 1-800-XXX-XXXX.

5.4 Respiratory Depression and Sleep-Disordered Breathing

Sodium oxybate may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported [*see Overdosage (10)*].

In a study assessing the respiratory-depressant effects of sodium oxybate at doses up to 9 g per night in 21 patients with narcolepsy, no dose-related changes in oxygen saturation were demonstrated in the group as a whole. One of the four

patients with preexisting, moderate-to-severe sleep apnea had significant worsening of the apnea/hypopnea index during treatment.

In a study assessing the effects of sodium oxybate 9 g per night in 50 patients with obstructive sleep apnea, sodium oxybate did not increase the severity of sleep-disordered breathing and did not adversely affect the average duration and severity of oxygen desaturation overall. However, there was a significant increase in the number of central apneas in patients taking sodium oxybate, and clinically significant oxygen desaturation ($\leq 55\%$) was measured in three patients (6%) after sodium oxybate administration, with one patient withdrawing from the study and two continuing after single brief instances of desaturation. Prescribers should be aware that increased central apneas and clinically relevant desaturation events have been observed with sodium oxybate administration.

In clinical trials in 128 patients with narcolepsy, two subjects had profound CNS depression, which resolved after supportive respiratory intervention. Two other patients discontinued sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea. In two controlled trials assessing polysomnographic (PSG) measures in patients with narcolepsy, 40 of 477 patients were included with a baseline apnea/hypopnea index of 16 to 67 events per hour, indicative of mild to severe sleep-disordered breathing. None of the 40 patients had a clinically significant worsening of respiratory function as measured by apnea/hypopnea index and pulse oximetry at doses of 4.5 g to 9 g per night.

Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients and in postmenopausal women not on hormone replacement therapy as well as among patients with narcolepsy.

5.5 Depression and Suicidality

In clinical trials in patients with narcolepsy (n=781), there were two suicides and two attempted suicides in sodium oxybate-treated patients, including three patients with a previous history of depressive psychiatric disorder. Of the two suicides, one patient used sodium oxybate in conjunction with other drugs. Sodium oxybate was not involved in the second suicide. Adverse reactions of depression were reported by 7% of 781 sodium oxybate-treated patients, with four patients (<1%) discontinuing because of depression. In most cases, no change in sodium oxybate treatment was required.

In a controlled trial, with patients randomized to fixed doses of 3 g, 6 g, or 9 g per night sodium oxybate or placebo, there was a single event of depression at the 3 g per night dose. In another controlled trial, with patients titrated from an initial 4.5 g per night starting dose, the incidences of depression were 1 (1.7%), 1 (1.5%), 2 (3.2%), and 2 (3.6%) for the placebo, 4.5 g, 6 g, and 9 g per night doses, respectively.

The emergence of depression in patients treated with sodium oxybate requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking sodium oxybate.

5.6 Other Behavioral or Psychiatric Adverse Reactions

During clinical trials in narcolepsy, 3% of 781 patients treated with sodium oxybate experienced confusion, with incidence generally increasing with dose.

Less than 1% of patients discontinued the drug because of confusion. Confusion was reported at all recommended doses from 6 g to 9 g per night. In a controlled trial where patients were randomized to fixed total daily doses of 3 g, 6 g, or 9 g per night or placebo, a dose-response relationship for confusion was demonstrated, with 17% of patients at 9 g per night experiencing confusion. In all cases in that controlled trial, the confusion resolved soon after termination of treatment. In Trial 3 where sodium oxybate was titrated from an initial 4.5 g per night dose, there was a single event of confusion in one patient at the 9 g per night dose. In the majority of cases in all clinical trials in narcolepsy, confusion resolved either soon after termination of dosing or with continued treatment. However, patients treated with sodium oxybate who become confused should be evaluated fully, and appropriate intervention considered on an individual basis.

Anxiety occurred in 5.8% of the 874 patients receiving sodium oxybate in clinical trials in another population. The emergence of or increase in anxiety in patients taking sodium oxybate should be carefully monitored.

Other neuropsychiatric reactions reported in sodium oxybate clinical trials included hallucinations, paranoia, psychosis, and agitation. The emergence of thought disorders and/or behavior abnormalities requires careful and immediate evaluation.

5.7 Parasomnias

Sleepwalking, defined as confused behavior occurring at night and at times associated with wandering, was reported in 6% of 781 patients with narcolepsy treated with sodium oxybate in controlled and long-term open-label studies, with <1% of patients discontinuing due to sleepwalking. Rates of sleepwalking were similar for patients taking placebo and patients taking sodium oxybate in controlled trials. It is unclear if some or all of the reported sleepwalking episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Five instances of significant injury or potential injury were associated with sleepwalking during a clinical trial of sodium oxybate in patients with narcolepsy.

Parasomnias including sleepwalking have been reported in postmarketing experience with sodium oxybate. Therefore, episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

5.8 Use in Patients Sensitive to High Sodium Intake

Sodium oxybate has a high salt content. In patients sensitive to salt intake (e.g., those with heart failure, hypertension, or renal impairment) consider the amount of daily sodium intake in each dose of sodium oxybate. Table 2 provides the approximate sodium content per sodium oxybate oral solution dose.

Table 2: Approximate Sodium Content per Total Nightly Dose of Sodium Oxybate (g = grams)

Sodium Oxybate Dose	Sodium Content/Total Nightly Exposure
3 g per night	550 mg
4.5 g per night	820 mg
6 g per night	1100 mg
7.5 g per night	1400 mg
9 g per night	1640 mg

6 ADVERSE REACTIONS

The following adverse reactions appear in other sections of the labeling:

- CNS depression [*see Warnings and Precautions (5.1)*]
- Abuse and Misuse [*see Warnings and Precautions (5.2)*]
- Respiratory Depression and Sleep-Disordered Breathing [*see Warnings and Precautions (5.4)*]
- Depression and Suicidality [*see Warnings and Precautions (5.5)*]
- Other Behavioral or Psychiatric Adverse Reactions [*see Warnings and Precautions (5.6)*]
- Parasomnias [*see Warnings and Precautions (5.7)*]
- Use in Patients Sensitive to High Sodium Intake [*see Warnings and Precautions (5.8)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Sodium oxybate was studied in three placebo-controlled clinical trials (Trials N1, N3, and N4, described in Sections 14.1 and 14.2) in 611 patients with narcolepsy (398 subjects treated with sodium oxybate, and 213 with placebo). A total of 781 patients with narcolepsy were treated with sodium oxybate in controlled and uncontrolled clinical trials.

Section 6.1 and Table 3 presents adverse reactions from three pooled, controlled trials (N1, N3, N4,) in patients with narcolepsy.

Adverse Reactions Leading to Treatment Discontinuation

Of the 398 sodium oxybate-treated patients with narcolepsy, 10.3% of patients discontinued because of adverse reactions compared with 2.8% of patients receiving placebo. The most common adverse reaction leading to discontinuation was nausea (2.8%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.

Commonly Observed Adverse Reactions in Controlled Clinical Trials

The most common adverse reactions (incidence $\geq 5\%$ and twice the rate seen with placebo) in sodium oxybate-treated patients were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.

Adverse Reactions Occurring at an Incidence of 2% or Greater

Table 3 lists adverse reactions that occurred at a frequency of 2% or more in any treatment group for three controlled trials and were more frequent in any sodium oxybate treatment group than with placebo. Adverse reactions are summarized by dose at onset. Nearly all patients in these studies initiated treatment at 4.5 g per night. In patients who remained on treatment, adverse reactions tended to occur early and to diminish over time.

Table 3: Adverse Reactions Occurring in $\geq 2\%$ of Patients and More Frequently with Sodium Oxybate than Placebo in Three Controlled Trials (N1, N3, N4) by Body System and Dose at Onset

System Organ Class/MedDRA Preferred Term	Placebo (n=213) %	Sodium Oxybate 4.5 g (n=185) %	Sodium Oxybate 6 g (n=258) %	Sodium Oxybate 9 g (n=178) %
ANY ADVERSE REACTION	62	45	55	70
Gastrointestinal Disorders				
Nausea	3	8	13	20
Vomiting	1	2	4	11
Diarrhea	2	4	3	4
Abdominal Pain Upper	2	3	1	2
Dry Mouth	2	1	2	1
General Disorders and Administrative Site Conditions				
Pain	1	1	<1	3
Feeling Drunk	1	0	<1	3
Edema Peripheral	1	3	0	0
Musculoskeletal and Connective Tissue Disorders				
Pain in Extremity	1	3	1	1
Cataplexy	1	1	1	2
Muscle Spasms	2	2	<1	2
Nervous System Disorders				
Dizziness	4	9	11	15
Somnolence	4	1	3	8
Tremor	0	0	2	5
Paresthesia	1	2	1	3
Disturbance in Attention	0	1	0	4
Sleep Paralysis	1	0	1	3
Psychiatric Disorders				
Disorientation	1	1	2	3

Anxiety	1	1	1	2
Irritability	1	0	<1	3
Sleep Walking	0	0	0	3
Renal and Urinary Disorders				
Enuresis	1	3	3	7
Skin and Subcutaneous Tissue Disorders				
Hyperhidrosis	0	1	1	3

Dose-Response Information

In clinical trials in narcolepsy, a dose-response relationship was observed for nausea, vomiting, paresthesia, disorientation, irritability, disturbance in attention, feeling drunk, sleepwalking, and enuresis. The incidence of all these reactions was notably higher at 9 g per night.

In controlled trials in narcolepsy, discontinuations of treatment due to adverse reactions were greater at higher doses of sodium oxybate.

6.2 Postmarketing Experience

The following additional adverse reactions that have a likely causal relationship to sodium oxybate exposure have been identified during postmarketing use of sodium oxybate. These adverse reactions include: arthralgia, decreased appetite, fall, fluid retention, hangover, headache, hypersensitivity, hypertension, memory impairment, panic attack, vision blurred, and weight decreased. Because these reactions are reported voluntarily, it is not always possible to reliably estimate their frequency.

7 DRUG INTERACTIONS

7.1 Alcohol, Sedative Hypnotics, and CNS Depressants

Sodium oxybate should not be used in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of sodium oxybate.

7.2 Divalproex Sodium

Concomitant use of sodium oxybate with divalproex sodium resulted in a 25% mean increase in systemic exposure to sodium oxybate (AUC ratio range of 0.8 to 1.7) and in a greater impairment on some tests of attention and working memory. An initial sodium oxybate dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking sodium oxybate [see *Dosage and Administration* (2.4); *Clinical Pharmacology* (12.3)]. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of sodium oxybate and divalproex sodium is warranted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Sodium oxybate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Oral administration of sodium oxybate to pregnant rats (150, 350, or 1,000 mg/kg/day) or rabbits (300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity. The highest doses tested in rats and rabbits were approximately 1 and 3 times, respectively, the maximum recommended human dose (MRHD) of 9 g per night on a body surface area (mg/m²) basis.

Oral administration of sodium oxybate (150, 350, or 1,000 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and body weight gain at the highest dose tested. The no-effect dose for pre- and postnatal developmental toxicity in rats is less than the MRHD on a mg/m² basis.

8.2 Labor and Delivery

Sodium oxybate has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate, newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid, but umbilical vein levels of sodium oxybate were no more than 25% of the maternal concentration. No sodium oxybate was detected in the infant's blood 30 minutes after delivery. Elimination curves of sodium oxybate between a 2-day-old infant and a 15-year-old patient were similar. Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown.

8.3 Nursing Mothers

It is not known whether sodium oxybate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sodium oxybate is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of sodium oxybate in patients with narcolepsy did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects. In controlled trials in another population, 39 (5%) of 874 patients were 65 years or older. Discontinuations of treatment due to adverse reactions were increased in the elderly compared to younger adults (20.5% v. 18.9%). Frequency of headaches was markedly increased in the elderly (38.5% v. 18.9%). The most common adverse reactions were similar in both age categories. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

The starting dose of sodium oxybate should be reduced by one-half in patients with liver impairment [*see Dosage and Administration (2.3); Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Sodium Oxybate Oral Solution is a Schedule III controlled substance under the Federal Controlled Substances Act. Non-medical use of sodium oxybate could lead to penalties assessed under the higher Schedule I controls.

9.2 Abuse

Sodium oxybate, the sodium salt of GHB, produces dose-dependent central nervous system effects, including hypnotic and positive subjective reinforcing effects. The onset of effect is rapid, enhancing its potential for abuse or misuse.

The rapid onset of sedation, coupled with the amnestic features of sodium oxybate, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).

Illicit GHB is abused in social settings primarily by young adults. Some of the doses estimated to be abused are in a similar dosage range to that used for treatment of patients with cataplexy. GHB has some commonalities with ethanol over a limited dose range, and some cross tolerance with ethanol has been reported as well. Cases of severe dependence and

craving for GHB have been reported when the drug is taken around the clock. Patterns of abuse indicative of dependence include: 1) the use of increasingly large doses, 2) increased frequency of use, and 3) continued use despite adverse consequences.

Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g. increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy). Dispose of sodium oxybate according to state and federal regulations. It is safe to dispose of sodium oxybate down the sanitary sewer.

9.3 Dependence

There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the therapeutic dose range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal, visual hallucinations, agitation, and delirium. These symptoms generally abated in 3 to 14 days. In cases of severe withdrawal, hospitalization may be required. The discontinuation effects of sodium oxybate have not been systematically evaluated in controlled clinical trials. In the clinical trial experience with sodium oxybate in narcolepsy/cataplexy patients at therapeutic doses, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time.

Tolerance

Tolerance to sodium oxybate has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended sodium oxybate dosage regimen. Clinical studies of sodium oxybate in the treatment of alcohol withdrawal suggest a potential cross-tolerance with alcohol. The safety and effectiveness of sodium oxybate in the treatment of alcohol withdrawal have not been established.

10 OVERDOSAGE

10.1 Human Experience

Information regarding overdose with sodium oxybate is derived largely from reports in the medical literature that describe symptoms and signs in individuals who have ingested GHB illicitly. In these circumstances the co-ingestion of other drugs and alcohol was common, and may have influenced the presentation and severity of clinical manifestations of overdose.

In clinical trials two cases of overdose with sodium oxybate were reported. In the first case, an estimated dose of 150 g, more than 15 times the maximum recommended dose, caused a patient to be unresponsive with brief periods of apnea and to be incontinent of urine and feces. This individual recovered without sequelae. In the second case, death was reported following a multiple drug overdose consisting of sodium oxybate and numerous other drugs.

10.2 Signs and Symptoms

Information about signs and symptoms associated with overdosage with sodium oxybate derives from reports of its illicit use. Patient presentation following overdose is influenced by the dose ingested, the time since ingestion, the co-ingestion of other drugs and alcohol, and the fed or fasted state. Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even when obtunded), diaphoresis, headache, and impaired psychomotor skills have been observed. No typical pupillary changes have been described to assist in diagnosis; pupillary reactivity to light is maintained. Blurred vision has been reported. An increasing depth of coma has been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported.

Respiration may be unaffected or compromised in rate and depth. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact.

10.3 Recommended Treatment of Overdose

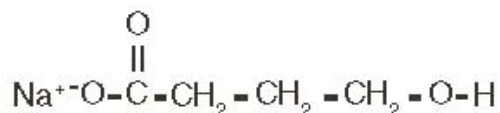
General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid-sequence induction (without the use of sedative) should be considered. Vital signs and consciousness should be closely monitored. The bradycardia reported with GHB overdose has been responsive to atropine intravenous administration. No reversal of the central depressant effects of sodium oxybate can be expected from naloxone or flumazenil administration. The use of hemodialysis and other forms of extracorporeal drug removal have not been studied in GHB overdose. However, due to the rapid metabolism of sodium oxybate, these measures are not warranted.

10.4 Poison Control Center

As with the management of all cases of drug overdosage, the possibility of multiple drug ingestion should be considered. The healthcare provider is encouraged to collect urine and blood samples for routine toxicologic screening, and to consult with a regional poison control center (1-800-222-1222) for current treatment recommendations.

11 DESCRIPTION

Sodium oxybate, a CNS depressant, is the active ingredient in Sodium Oxybate Oral Solution. The chemical name for sodium oxybate is sodium 4-hydroxybutyrate. The molecular formula is $C_4H_7NaO_3$, and the molecular weight is 126.09 g/mole. The chemical structure is:



Sodium oxybate is a white to off-white, crystalline powder that is very soluble in aqueous solutions. Each mL of Sodium Oxybate Oral Solution contains 0.5 g of sodium oxybate in purified water, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sodium oxybate is a CNS depressant. The mechanism of action of sodium oxybate in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of gamma hydroxybutyrate, an endogenous compound and metabolite of the neurotransmitter 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.

12.3 Pharmacokinetics

Pharmacokinetics of sodium oxybate are nonlinear and are similar following single or repeat dosing.

Absorption

Following oral administration, sodium oxybate is absorbed rapidly across the clinical dose range, with an absolute bioavailability of about 88%. The average peak plasma concentrations (C_{max}) following administration of each of the two 2.25 g doses given under fasting conditions 4 hours apart were similar. The average time to peak plasma concentration

(T_{max}) ranged from 0.5 to 1.25 hours. Following oral administration, the plasma levels of sodium oxybate increased more than dose-proportionally, with blood levels increasing 3.7-fold as total daily dose is doubled from 4.5 g to 9 g. Single doses greater than 4.5 g have not been studied. Administration of sodium oxybate immediately after a high-fat meal resulted in delayed absorption (average T_{max} increased from 0.75 hr to 2 hr) and a reduction in C_{max} by a mean of 59% and of systemic exposure (AUC) by 37%.

Distribution

Sodium oxybate is a hydrophilic compound with an apparent volume of distribution averaging 190 mL/kg to 384 mL/kg. At sodium oxybate concentrations ranging from 3 mcg/mL to 300 mcg/mL, less than 1% is bound to plasma proteins.

Metabolism

Animal studies indicate that metabolism is the major elimination pathway for sodium oxybate, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by beta-oxidation. The primary pathway involves a cytosolic NADP⁺-linked enzyme, GHB dehydrogenase, that catalyzes the conversion of sodium oxybate to succinic semialdehyde, which is then biotransformed to succinic acid by the enzyme succinic semialdehyde dehydrogenase. Succinic acid enters the Krebs cycle where it is metabolized to carbon dioxide and water. A second mitochondrial oxidoreductase enzyme, a transhydrogenase, also catalyzes the conversion to succinic semialdehyde in the presence of α -ketoglutarate. An alternate pathway of biotransformation involves β -oxidation via 3,4-dihydroxybutyrate to carbon dioxide and water. No active metabolites have been identified.

Elimination

The clearance of sodium oxybate is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. On average, less than 5% of unchanged drug appears in human urine within 6 to 8 hours after dosing. Fecal excretion is negligible. Sodium oxybate has an elimination half-life of 0.5 to 1 hour.

Specific Populations

Geriatric

There is limited experience with sodium oxybate in the elderly. Results from a pharmacokinetic study (n=20) in another studied population indicate that the pharmacokinetic characteristics of sodium oxybate are consistent among younger (age 48 to 64 years) and older (age 65 to 75 years) adults.

Pediatric

The pharmacokinetics of sodium oxybate in patients younger than 18 years of age have not been studied.

Gender

In a study of 18 female and 18 male healthy adult volunteers, no gender differences were detected in the pharmacokinetics of sodium oxybate oral solution following a single oral dose of 4.5 g.

Race

There are insufficient data to evaluate any pharmacokinetic differences among races.

Renal Impairment

No pharmacokinetic study in patients with renal impairment has been conducted.

Hepatic Impairment

The pharmacokinetics of sodium oxybate in 16 cirrhotic patients, half without ascites (Child's Class A) and half with ascites (Child's Class C), were compared to the kinetics in 8 subjects with normal hepatic function after a single oral dose

of 25 mg/kg. AUC values were double in the cirrhotic patients, with apparent oral clearance reduced from 9.1 mL/min/kg in healthy adults to 4.5 and 4.1 mL/min/kg in Class A and Class C patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control patients (mean $t_{1/2}$ of 59 and 32 minutes, respectively, versus 22 minutes). The starting dose of sodium oxybate should be reduced by one-half in patients with liver impairment [see *Dosage and Administration* (2.3); *Use in Specific Populations* (8.6)].

Drug Interactions Studies

Studies *in vitro* with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A up to the concentration of 3 mM (378 mcg/mL), a level considerably higher than levels achieved with therapeutic doses.

Drug interaction studies in healthy adults (age 18 to 50 years) were conducted with sodium oxybate and divalproex sodium, diclofenac, and ibuprofen:

- Divalproex sodium: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with divalproex sodium (valproic acid, 1250 mg per day) increased mean systemic exposure to sodium oxybate as shown by AUC by approximately 25%, while C_{max} was comparable. Co-administration did not appear to affect the pharmacokinetics of valproic acid. A greater impairment on some tests of attention and working memory was observed with co-administration of both drugs than with either drug alone [see *Drug Interactions* (7.2); *Dosage and Administration* (2.4)].
- Diclofenac: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with diclofenac (50 mg/dose twice per day) showed no significant differences in systemic exposure to sodium oxybate. Co-administration did not appear to affect the pharmacokinetics of diclofenac.
- Ibuprofen: Co-administration of sodium oxybate (6 g per day as two equal doses of 3 grams dosed four hours apart) with ibuprofen (800 mg/dose four times per day also dosed four hours apart) resulted in comparable systemic exposure to sodium oxybate as shown by plasma C_{max} and AUC values. Co-administration did not affect the pharmacokinetics of ibuprofen.

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, and modafinil. Also, there were no pharmacokinetic interactions with the alcohol dehydrogenase inhibitor fomepizole. However, pharmacodynamic interactions with these drugs cannot be ruled out. Alteration of gastric pH with omeprazole produced no significant change in the oxybate kinetics. In addition, drug interaction studies in healthy adults demonstrated no pharmacokinetic or clinically significant pharmacodynamic interactions between sodium oxybate and the SNRI duloxetine HCl.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Administration of sodium oxybate to rats at oral doses of up to 1,000 mg/kg/day for 83 (males) or 104 (females) weeks resulted in no increase in tumors. Plasma exposure (AUC) at the highest dose tested was 2 times that in humans at the maximum recommend human dose (MRHD) of 9 g per night.

The results of 2-year carcinogenicity studies in mouse and rat with gamma-butyrolactone, a compound that is metabolized to sodium oxybate *in vivo*, showed no clear evidence of carcinogenic activity. The plasma AUCs of sodium oxybate achieved at the highest doses tested in these studies were less than that in humans at the MRHD.

Mutagenesis

Sodium oxybate was negative in the *in vitro* bacterial gene mutation assay, an *in vitro* chromosomal aberration assay in mammalian cells, and in an *in vivo* rat micronucleus assay.

Impairment of Fertility

Oral administration of sodium oxybate (150, 350, or 1,000 mg/kg/day) to male and female rats prior to and throughout mating and continuing in females through early gestation resulted in no adverse effects on fertility. The highest dose tested is approximately equal to the MRHD on a mg/m² basis.

14 CLINICAL STUDIES

14.1 Cataplexy in Narcolepsy

The effectiveness of sodium oxybate in the treatment of cataplexy was established in two randomized, double-blind, placebo-controlled, multicenter, parallel-group trials (Trials N1 and N2) in patients with narcolepsy (see Table 4). In Trials N1 and N2, 85% and 80% of patients, respectively, were also being treated with CNS stimulants. The high percentages of concomitant stimulant use make it impossible to assess the efficacy and safety of sodium oxybate independent of stimulant use. In each trial, the treatment period was 4 weeks and the total nightly sodium oxybate doses ranged from 3 g to 9 g, with the total nightly dose administered as two equal doses. The first dose each night was taken at bedtime and the second dose was taken 2.5 to 4 hours later. There were no restrictions on the time between food consumption and dosing.

Trial N1 enrolled 136 narcoleptic patients with moderate to severe cataplexy (median of 21 cataplexy attacks per week) at baseline. Prior to randomization, medications with possible effects on cataplexy were withdrawn, but stimulants were continued at stable doses. Patients were randomized to receive placebo, sodium oxybate 3 g per night, sodium oxybate 6 g per night, or sodium oxybate 9 g per night.

Trial N2 was a randomized withdrawal trial with 55 narcoleptic patients who had been taking open-label sodium oxybate for 7 to 44 months prior to study entry. To be included, patients were required to have a history of at least 5 cataplexy attacks per week prior to any treatment for cataplexy. Patients were randomized to continued treatment with sodium oxybate at their stable dose (ranging from 3 g to 9 g per night) or to placebo for 2 weeks. Trial N2 was designed specifically to evaluate the continued efficacy of sodium oxybate after long-term use.

The primary efficacy measure in Trials N1 and N2 was the frequency of cataplexy attacks.

Table 4: Median Number of Cataplexy Attacks in Trials N1 and N2

Trial/Dosage Group	Baseline	Median Change From Baseline	Comparison to Placebo (p-value)
Trial N1 (Prospective, Randomized, Parallel Group Trial)			
		(median attacks/week)	
Placebo (n=33)	20.5	-4	-
Sodium oxybate 6 g per night (n=31)	23.0	-10	0.0451
Sodium oxybate 9 g per night (n=33)	23.5	-16	0.0016
Trial N2 (Randomized Withdrawal Trial)			
		(median attacks/2 weeks)	
Placebo (n=29)	4.0	21	-
Sodium oxybate (n=26)	1.9	0	<0.001

In Trial N1, both the 6 g and 9 g per night sodium oxybate doses resulted in statistically significant reductions in the frequency of cataplexy attacks. The 3 g per night dose had little effect. In Trial N2, patients randomized to placebo after discontinuing long-term open-label sodium oxybate therapy experienced a significant increase in cataplexy attacks ($p < 0.001$), providing evidence of long-term efficacy of sodium oxybate. In Trial N2, the response was numerically similar for patients treated with doses of 6 g to 9 g per night, but there was no effect seen in patients treated with doses less than 6 g per night, suggesting little effect at these doses.

14.2 Excessive Daytime Sleepiness in Narcolepsy

The effectiveness of sodium oxybate in the treatment of excessive daytime sleepiness in patients with narcolepsy was established in two randomized, double-blind, placebo-controlled trials (Trials N3 and N4) (see Tables 5 to 7). Seventy-eight percent of patients in Trial N3 were also being treated with CNS stimulants.

Trial N3 was a multicenter randomized, double-blind, placebo-controlled, parallel-group trial that evaluated 228 patients with moderate to severe symptoms at entry into the study including a median Epworth Sleepiness Scale (see below) score of 18, and a Maintenance of Wakefulness Test (see below) score of 8.3 minutes. Patients were randomized to one of 4 treatment groups: placebo, sodium oxybate 4.5 g per night, sodium oxybate 6 g per night, or sodium oxybate 9 g per night. The period of double-blind treatment in this trial was 8 weeks. Antidepressants were withdrawn prior to randomization; stimulants were continued at stable doses.

The primary efficacy measures in Trial N3 were the Epworth Sleepiness Scale and the Clinical Global Impression of Change. The Epworth Sleepiness Scale is intended to evaluate the extent of sleepiness in everyday situations by asking the patient a series of questions. In these questions, patients were asked to rate their chances of dozing during each of 8 activities on a scale from 0-3 (0=never; 1=slight; 2=moderate; 3=high). Higher total scores indicate a greater tendency to sleepiness. The Clinical Global Impression of Change is evaluated on a 7-point scale, centered at *No Change*, and ranging from *Very Much Worse* to *Very Much Improved*. In Trial N3, patients were rated by evaluators who based their assessments on the severity of narcolepsy at baseline.

In Trial N3, statistically significant improvements were seen on the Epworth Sleepiness Scale score at Week 8 and on the Clinical Global Impression of Change score at Week 8 with the 6 g and 9 g per night doses of sodium oxybate compared to the placebo group.

Table 5: Change From Baseline in Daytime Sleepiness Score (Epworth Sleepiness Scale) at Week 8 in Trial N3 (Range 0 to 24)

Treatment Group	Baseline	Week 8	Median Change From Baseline at Week 8	p-value
Placebo (n=59)	17.5	17.0	-0.5	-
Sodium oxybate 6 g per night (n=58)	19.0	16.0	-2.0	<0.001
Sodium oxybate 9 g per night (n=47)	19.0	12.0	-5.0	<0.001

Table 6: Proportion of Patients with a Very Much or Much Improved Clinical Global Impression of Change in Daytime and Nighttime Symptoms in Trial N3

Treatment Group	Percentages of Responders (Very Much Improved or Much Improved)	Change From Baseline Significance Compared to Placebo (p-value)
Placebo (n=59)	22%	-
Sodium oxybate 6 g per night (n=58)	52%	<0.001
Sodium oxybate 9 g per night (n=47)	64%	<0.001

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, sodium oxybate, modafinil, or sodium oxybate plus modafinil. Sodium oxybate 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 sodium oxybate plus modafinil treatment groups at the patient's prior dose. Trial N4 was not designed to compare the effects of sodium oxybate to modafinil because patients receiving modafinil were not titrated to a maximal dose. Patients randomized to placebo or to sodium oxybate 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 sodium oxybate and sodium oxybate plus modafinil groups compared to the placebo group.

This trial was not designed to compare the effects of sodium oxybate to modafinil, because patients receiving modafinil were not titrated to a maximally effective dose.

Table 7: Change in Baseline in the Maintenance of Wakefulness Test Score (in minutes) at Week 8 in Trial N4

Treatment Group	Baseline	Week 8	Mean Change From Baseline at Week 8	p-value
Placebo (modafinil withdrawn) (n=55)	9.7	6.9	-2.7	-
Sodium oxybate (modafinil withdrawn) (n=50)	11.3	12.0	0.6	<0.001
Sodium oxybate plus modafinil (n=54)	10.4	13.2	2.7	<0.001

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Sodium Oxybate Oral Solution is a clear to slightly opalescent oral solution. It is supplied in kits containing one bottle of Sodium Oxybate Oral Solution, a press-in-bottle adaptor, a 10 mL oral measuring device (plastic syringe), a Medication Guide and a professional insert. Two 75 mL dosing cups with child-resistant caps are included with each Sodium Oxybate Oral Solution shipment. Each white oblong HDPE bottle contains 180 mL of Sodium Oxybate Oral Solution at a concentration of 500 mg/mL and is sealed with a child resistant cap.

NDC 0054-0314-57: Each tamper evident single unit carton contains one 180 mL bottle (500 mg/mL) of Sodium Oxybate Oral Solution, one press-in-bottle adaptor and one oral dispensing syringe

16.2 Storage

Keep out of reach of children.

Store at 25°C (77°F); excursions permitted up to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.

Solutions prepared following dilution should be consumed within 24 hours.

16.3 Handling and Disposal

Sodium Oxybate Oral Solution is a Schedule III drug under the Controlled Substances Act. Sodium oxybate should be handled according to state and federal regulations. It is safe to dispose of sodium oxybate down the sanitary sewer.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Sodium Oxybate REMS Program

- Inform patients that sodium oxybate is available only through the Sodium Oxybate REMS Program.
- The contents of the sodium oxybate Medication Guide and educational materials are reviewed with every patient before initiating treatment with sodium oxybate.
- Patients must read and understand the materials in the Sodium Oxybate REMS Program prior to initiating treatment. Inform the patient that they should be seen by the prescriber frequently to review dose titration, symptom response, and adverse reactions; a follow-up of every three months is recommended.
- Discuss safe and proper use of sodium oxybate and dosing information with patients prior to the initiation of treatment. Instruct patients to store sodium oxybate bottles and sodium oxybate doses in a secure place, out of the reach of children and pets.

Alcohol or Sedative Hypnotics

Advise patients not to drink alcohol or take other sedative hypnotics if they are taking sodium oxybate.

Sedation

Inform patients that after taking sodium oxybate they are likely to fall asleep quickly (often within 5 and usually within 15 minutes), but the time it takes to fall asleep can vary from night to night. The sudden onset of sleep, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization. Instruct patients to remain in bed following ingestion of their first and second doses. Instruct patients not to take their second dose until 2.5 to 4 hours after the first dose.

Food Effects on Sodium Oxybate

Inform patients to take the first dose at least 2 hours after eating.

Respiratory Depression

Inform patients that sodium oxybate can be associated with respiratory depression.

Operating Hazardous Machinery

Inform patients that until they are reasonably certain that sodium oxybate does not affect them adversely (e.g., impair judgment, thinking, or motor skills) they should not operate hazardous machinery, including automobiles or airplanes.

Suicidality

Instruct patients or families to contact a healthcare provider immediately if the patient develops depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or suicidal ideation.

Sleepwalking

Instruct patients and their families that sodium oxybate has been associated with sleepwalking and to contact their healthcare provider if this occurs.

Sodium Intake

Instruct patients who are sensitive to salt intake (e.g., those with heart failure, hypertension, or renal impairment) that sodium oxybate contains a significant amount of sodium and they should limit their sodium intake.

Medication Guide - Sodium Oxybate (soe' dee um ox' i bate) Oral Solution, CIII

Read this Medication Guide carefully before you start taking sodium oxybate and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about sodium oxybate?

Sodium oxybate can cause serious side effects including slow breathing or changes in your alertness. Do not drink alcohol or take medicines intended to make you fall asleep while you are taking sodium oxybate because they can make these side effects worse. Call your doctor right away if you have any of these serious side effects.

- The active ingredient of Sodium Oxybate Oral Solution is a form of gamma-hydroxybutyrate (GHB). GHB is a chemical that has been abused and misused. Abuse and misuse of sodium oxybate can cause serious medical problems, including:
 - seizures
 - trouble breathing
 - changes in alertness
 - coma
 - death
- Do not drive a car, use heavy machinery, fly an airplane, or do anything that is dangerous or that requires you to be fully awake for at least 6 hours after you take sodium oxybate. You should not do those activities until you know how sodium oxybate affects you.
- Sodium oxybate is available only by prescription and filled through the Sodium Oxybate REMS Program. Before you receive sodium oxybate, your doctor or pharmacist will make sure that you understand how to use sodium oxybate safely and effectively. If you have any questions about sodium oxybate, ask your doctor or call the Sodium Oxybate REMS Program at 1-800-XXX-XXXX.

What is sodium oxybate?

Sodium oxybate is a prescription medicine used to treat the following symptoms in people who fall asleep frequently during the day, often at unexpected times (narcolepsy):

- suddenly weak or paralyzed muscles when they feel strong emotions (cataplexy)
- excessive daytime sleepiness (EDS) in people who have narcolepsy

It is not known if sodium oxybate is safe and effective in children.

Sodium Oxybate Oral Solution is a controlled substance (CIII) because it contains sodium oxybate that can be a target for people who abuse prescription medicines or street drugs. Keep your sodium oxybate in a safe place to protect it from theft. Never give your sodium oxybate to anyone else because it may cause death or harm them. Selling or giving away this medicine is against the law.

Who should not take sodium oxybate?

Do not take sodium oxybate if you:

- take other sleep medicines or sedatives (medicines that cause sleepiness)
- drink alcohol
- have a rare problem called succinic semialdehyde dehydrogenase deficiency

Before you take sodium oxybate, tell your doctor if you:

- have short periods of not breathing while you sleep (sleep apnea).
- snore, have trouble breathing, or have lung problems. You may have a higher chance of having serious breathing problems when you take sodium oxybate.
- have or had depression or have tried to harm yourself. You should be watched carefully for new symptoms of depression.
- have liver problems.
- are on a salt-restricted diet. Sodium oxybate contains a lot of sodium (salt) and may not be right for you.
- have high blood pressure.
- have heart failure.
- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if sodium oxybate can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if sodium oxybate passes into your breast milk. You and your doctor should decide if you will take sodium oxybate or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially, tell your doctor if you take other medicines to help you sleep (sedatives). Do not take medicines that make you sleepy with sodium oxybate.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take sodium oxybate?

- Read the **Instructions for Use** at the end of this Medication Guide for detailed instructions on how to take sodium oxybate.
- Take sodium oxybate exactly as your doctor tells you to take it.
- Never change your sodium oxybate dose without talking to your doctor.
- Sodium oxybate can cause sleep very quickly. You should fall asleep soon. Some patients fall asleep within 5 minutes and most fall asleep within 15 minutes. Some patients take less time to fall asleep and some take more time. The time it takes you to fall asleep might be different from night to night.
- Take your first sodium oxybate dose at bedtime while you are in bed. Take your second sodium oxybate dose 2.5 to 4 hours after you take your first sodium oxybate dose. You may want to set an alarm clock to make sure you wake up to take your second sodium oxybate dose. You should remain in bed after taking the first and second doses of sodium oxybate.
- If you miss your second sodium oxybate dose, skip that dose and do not take sodium oxybate again until the next night. Never take 2 sodium oxybate doses at 1 time.
- Wait at least 2 hours after eating before you take sodium oxybate.
- You should see your doctor every 3 months for a check-up while taking sodium oxybate. Your doctor should check to see if sodium oxybate is helping to lessen your symptoms and if you feel any side effects while you take sodium oxybate.

- If you take too much sodium oxybate, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of sodium oxybate?

Sodium oxybate can cause serious side effects, including:

- See **“What is the most important information I should know about sodium oxybate?”**
- **Breathing problems, including:**
 - slower breathing
 - trouble breathing
 - short periods of not breathing while sleeping (sleep apnea). People who already have breathing or lung problems have a higher chance of having breathing problems when they use sodium oxybate.
- **Mental health problems, including:**
 - confusion
 - seeing or hearing things that are not real (hallucinations)
 - unusual or disturbing thoughts (abnormal thinking)
 - feeling anxious or upset
 - depression
 - thoughts of killing yourself or trying to kill yourself

Call your doctor right away if you have symptoms of mental health problems.

- **Sleepwalking.** Sleepwalking can cause injuries. Call your doctor if you start sleepwalking. Your doctor should check you.

The most common side effects of sodium oxybate include:

- nausea
- dizziness
- vomiting
- bedwetting
- diarrhea

Your side effects may increase when you take higher doses of sodium oxybate. Sodium oxybate can cause physical dependence and craving for the medicine when it is not taken as directed.

These are not all the possible side effects of sodium oxybate. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store sodium oxybate?

- **Always store sodium oxybate in the original bottle or in the dosing cups with child-resistant caps provided with your prescription.**
- **Keep sodium oxybate in a safe place out of the reach of children and pets.**
- **Get emergency medical help right away if a child drinks your sodium oxybate.**
- Store sodium oxybate between 68°F to 77°F (20°C to 24°C). When you have finished using a sodium oxybate bottle:
 - empty any unused sodium oxybate down the sink drain
 - cross out the label on the sodium oxybate bottle with a marker
 - place the empty sodium oxybate bottle in the trash

General information about the safe and effective use of sodium oxybate

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use sodium oxybate for a condition for which it was not prescribed. Do not give sodium oxybate to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about sodium oxybate. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about sodium oxybate that is written for health professionals.

For more information, call the Sodium Oxybate REMS Program at 1-800-XXX-XXXX.

What are the ingredients in Sodium Oxybate Oral Solution?

Active Ingredients: sodium oxybate

Inactive Ingredients: purified water, USP

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Instructions for Use - Sodium Oxybate (soe' dee um ox' i bate) Oral Solution, CIII

Read these Instructions for Use carefully before you start taking sodium oxybate and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

Note:

- **You will need to split your prescribed sodium oxybate dose into 2 separate dosing cups for mixing (provided with your prescription).**
- **You will need to mix sodium oxybate with water before you take your dose.**
- **Take your dose within 24 hours after mixing sodium oxybate with water. If you do not take your dose within this time, you will need to throw the mixture away.**

Supplies you will need for mixing and taking sodium oxybate: See Figure A.

- bottle of your sodium oxybate medicine
- press-in-bottle adaptor with straw attached
- syringe for drawing up your sodium oxybate dose
- a measuring cup containing about 1/4 cup of water (not provided with your sodium oxybate prescription)
- 2 **empty** dosing cups with child-resistant caps
- alarm clock by your bedside (not provided with your sodium oxybate prescription)

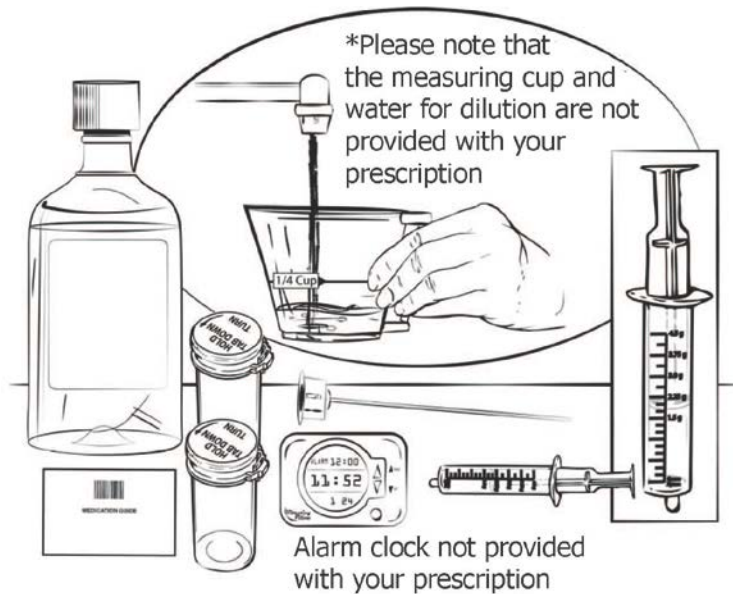


Figure A

Step 1. Take the sodium oxybate bottle, press-in-bottle adaptor, and syringe out of the box.

Step 2. Remove the bottle cap from the sodium oxybate bottle by pushing down while turning the cap counterclockwise (to the left). See Figure B.

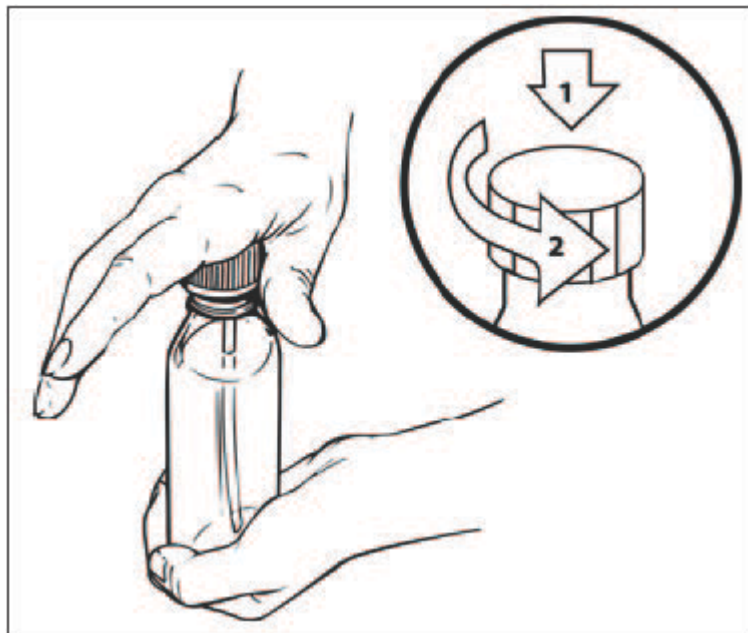


Figure B

Step 3.

- The press-in-bottle adaptor may already be put in place by the pharmacy. If it is not already in place, you will have to do it yourself. After removing the cap from the sodium oxybate bottle, set the bottle upright on a tabletop.
- While holding the sodium oxybate bottle in its upright position, insert the press-in-bottle adaptor into the neck of the sodium oxybate bottle. See Figure C.



Figure C

- Tilt the straw toward the edge of the bottom of the bottle to be sure you can draw out your dose of the medicine. You only need to do this the first time you open the bottle. See Figure D.



Figure D

- After you draw out your dose of the medicine, leave the adaptor in the bottle for all your future uses. See Figure E.

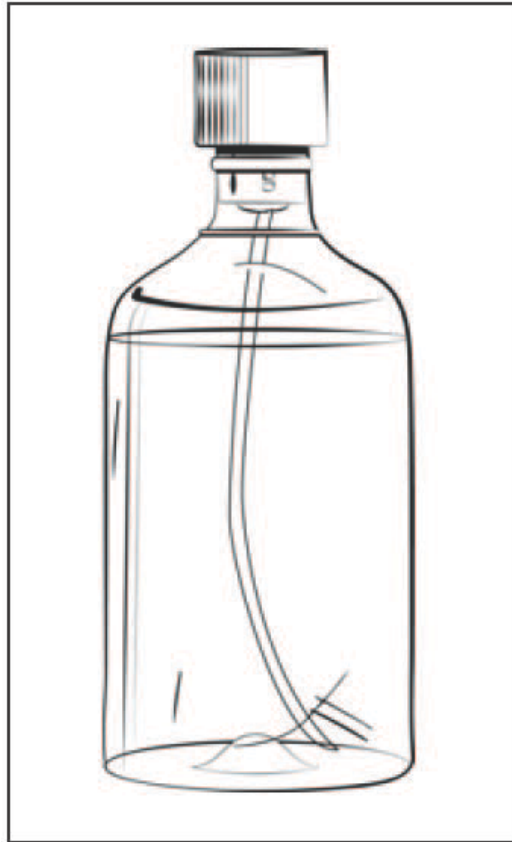


Figure E

Step 4.

- Take the syringe out of the plastic wrapper. Use only the syringe provided with your sodium oxybate prescription.
- While holding the sodium oxybate bottle upright on the tabletop, insert the tip of the syringe into the opening on top of the sodium oxybate bottle and press down firmly. See Figure F.

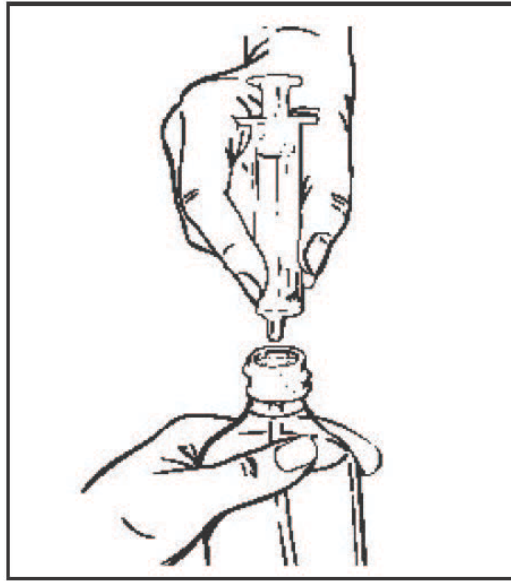


Figure F

Step 5.

- Hold the bottle and syringe down with one hand, and draw up one-half (1/2) of your total prescribed nightly dose with the other hand by pulling up on the plunger. For example, if your total nightly dose of sodium oxybate is 4.5 grams a night, you will need to draw up 2 separate doses of 2.25 grams each, one for each dosing cup. See Figure G.

Note: The sodium oxybate medicine will not flow into the syringe unless you keep the bottle upright.

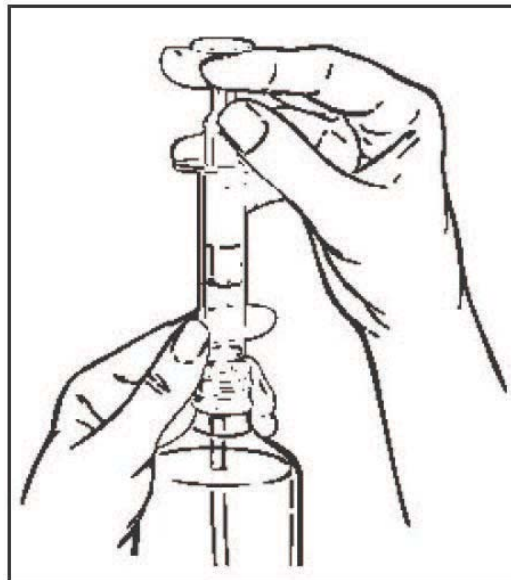


Figure G

Step 6.

- After you draw up each separate sodium oxybate dose, remove the syringe from the opening of the sodium oxybate bottle. Put the tip into 1 of the **empty** dosing cups with child-resistant caps.
- **Make sure the dosing cup is empty and does not contain any medicine from your previous night's dose.**

- Empty each separate sodium oxybate dose into 1 of the **empty** dosing cups by pushing down on the plunger. (See Figure H).
- Using a measuring cup, pour about 1/4 cup of water into **each** dosing cup. **Be careful to add only water to each dosing cup and not more sodium oxybate. All shipped bottles of sodium oxybate contain the concentrated medicine. Water for mixing the medicine is not provided in the shipment.**

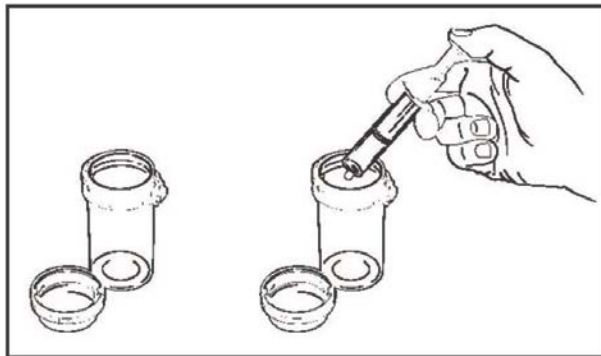


Figure H

Step 7.

- Place the child-resistant caps provided on the filled dosing cups and turn each cap clockwise (to the right) until it clicks and locks into its child-resistant position. See Figure I.

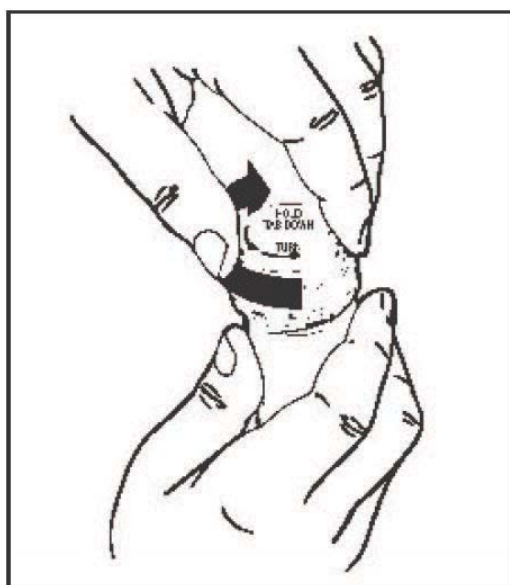


Figure I

- Put the cap back on the sodium oxybate bottle and store it in a safe and secure place. Store in a locked place if needed. Keep sodium oxybate out of the reach of children and pets.
- Rinse the syringe out with water and squirt the liquid into the sink drain.

Step 8.

- At bedtime, and before you take your first sodium oxybate dose, put your second sodium oxybate dose in a safe place near your bed.
- You may want to set an alarm clock to make sure you wake up to take the second dose.

- When it is time to take your first sodium oxybate dose, remove the cap from the dosing cup by pressing down on the child-resistant locking tab and turning the cap counterclockwise (to the left).
- Drink all of your first sodium oxybate dose at bedtime. Put the cap back on the first dosing cup before lying down to sleep.
- You should fall asleep soon. Some patients fall asleep within 5 minutes and most fall asleep within 15 minutes. Some patients take less time to fall asleep, and some take more time. The time it takes you to fall asleep might be different from night to night.

Step 9.

- When you wake up 2.5 to 4 hours later, take the cap off the second dosing cup.
- If you wake up before the alarm and it has been at least 2.5 hours since your first sodium oxybate dose, turn off your alarm and take your second sodium oxybate dose.
- While sitting in bed, drink all of the second sodium oxybate dose and put the cap back on the second dosing cup before lying down to continue sleeping.

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