PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[C] XYREM®

sodium oxybate oral solution

500 mg/mL

CNS Depressant

Jazz Pharmaceuticals Ireland Limited
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XYREM®

Sodium oxybate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Liquid 500 mg/mL	Water, malic acid

INDICATIONS AND CLINICAL USE

Xyrem (sodium oxybate) oral solution is indicated for the treatment of cataplexy in patients with narcolepsy.

In Xyrem clinical trials, approximately 80% of patients maintained concomitant stimulant use (see **BLACK BOX WARNING**).

Xyrem should only be prescribed by physicians who meet the following requirements: i) Experience in treating cataplexy in patients with narcolepsy; ii) Completion of the Xyrem Physician Success Program.

The Xyrem Success Program is a Risk Management Program founded on the following core components that provide for the safe and effective use of the drug, and limit the potential for drug diversion and abuse:

i) Implementation of a program to educate physicians, pharmacists and patients about the risks and benefits of XYREM, including critical information necessary for the safe use, storage and handling of the drug.
ii) Implementation of a restricted distribution program for Xyrem through a single wholesale distribution company that will ship the drug directly to pharmacies on an as-needed basis after patients have presented with an initial legitimate prescription.
iii) Filling of the initial prescription only after the prescriber, pharmacist and patient have received and read the educational materials.
iv) Maintenance of a registry of Xyrem Success Program trained physicians, pharmacies and patients.

Xyrem is not recommended for use in other indications as safety and efficacy has not been established outside of cataplexy.

Physicians may obtain more information about the Xyrem Success Program by calling the following toll-free phone number: 1-866-5XYREM5 (1-866-599-7365).

Geriatrics (> 65 years of age):
The pharmacokinetics of sodium oxybate in patients greater than the age of 65 years have not been studied (see ***Special Populations*** in **WARNINGS AND PRECAUTIONS**).

Pediatrics (< 18 years of age):
The pharmacokinetics of sodium oxybate in patients under the age of 18 years have not been studied (see ***Special Populations*** in **WARNINGS AND PRECAUTIONS**).

CONTRAINDICATIONS

Xyrem is contraindicated in patients who are hypersensitive to sodium oxybate or to any ingredient in the formulation.

Concurrent use of Xyrem (sodium oxybate) with sedative hypnotic agents or alcohol is contraindicated.

Xyrem is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency. This rare disorder is an inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
WARNING: Central nervous system depressant with abuse potential.
Should not be used with alcohol or other CNS depressants.

Sodium oxybate is gamma-hydroxybutyrate (GHB), a known drug of abuse that has been associated with some important central nervous system (CNS) adverse events, including death in abuse situations. Even at recommended doses, use has been associated with confusion, depression and other neuropsychiatric events. Reports of respiratory depression occurred in clinical trials. Most patients receiving sodium oxybate during clinical trials maintained concomitant stimulant use.

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)

Under the Xyrem Success Program, Xyrem is made available to prescribers and pharmacists through a single wholesaler. Educational materials for physicians and pharmacists are available through the wholesaler (1-866-5XYREM5 (1-866-599-7365)). Physicians are required to read the materials prior to prescribing Xyrem. Educational materials are also available for patients, who should confirm that they have read and understood the materials.

The Xyrem Success Program includes recommendations for educating patients and information to help minimize the risks of inadvertent use by others. These recommendations encourage physicians to see their patients every 3 months during the course of therapy and to report all serious adverse events to the manufacturer.

Xyrem is approved for use only in the treatment of cataplexy in patients with narcolepsy.

Xyrem (sodium oxybate) should only be ingested at bedtime. For at least 6 hours after ingesting sodium oxybate, patients must not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery, driving a motor vehicle, or flying an airplane. When patients first start taking Xyrem or any other sleep medicine, until they know whether the medicine will still have some carryover effect on them the next day, they should use extreme caution while performing any task that could be dangerous or requires full mental alertness.

The combined use of alcohol (ethanol) with sodium oxybate may result in potentiation of

the central nervous system-depressant effects of sodium oxybate. Therefore, patients should be warned to avoid the use of any alcoholic beverage in conjunction with sodium oxybate (see CONTRAINDICATIONS).

Sodium oxybate should not be used in combination with sedative hypnotics or other CNS depressants including sedating anti-epileptic drugs (AEDs).

Central Nervous System Depression/Respiratory Depression
Sodium oxybate is a CNS depressant with the potential to impair respiratory drive, especially in patients with already-compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported (see **OVERDOSAGE**).

Patients should be warned against the use of sodium oxybate in conjunction with other CNS depressants. The concurrent use of Xyrem 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. In addition, there have been clinical observations of coma and increased plasma GHB concentration after co-administration of sodium oxybate with topiramate.

If use of these CNS depressants in combination with Xyrem is required, dose reduction or discontinuation of one or more CNS depressants (including Xyrem) should be considered. In addition, if short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with Xyrem should be considered.

In clinical trials, two subjects had profound CNS depression. A 39 year-old woman, a healthy volunteer received a single 4.5 g dose of sodium oxybate after fasting for 10 hours. An hour later, while asleep, she developed decreased respiration and was treated with an oxygen mask. An hour later, this event recurred. She also vomited and had fecal incontinence. In another case, a 64 year-old narcoleptic man was found unresponsive on the floor on Day 170 of treatment with sodium oxybate at a total daily dose of 4.5 g/night. Two other patients discontinued sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea.

The respiratory depressant effects of Xyrem, at recommended doses, were assessed in 21 patients with narcolepsy, and no dose-related changes in oxygen saturation were demonstrated in the group as a whole. One of these patients had significant concomitant pulmonary illness, and 4 of the 21 had moderate-to-severe sleep apnea. One of the 4 patients with sleep apnea had significant worsening of the apnea/hypopnea index during treatment, but worsening did not increase at higher doses. Another patient discontinued treatment because of a perceived increase in clinical apnea events. Caution should be observed if Xyrem is prescribed to patients with compromised respiratory function. Prescribers should be aware that sleep apnea has been reported with a high incidence (even 50%) in some cohorts of narcoleptic patients.

Confusion/Neuropsychiatric Adverse Events
During clinical trials, 7% of patients treated with sodium oxybate experienced confusion. Fewer than 1% of patients discontinued the drug because of confusion. In all cases, the confusion

resolved soon after termination of treatment. In the majority of cases, confusion resolved with continued treatment. Patients treated with Xyrem who become confused should be evaluated fully, and appropriate intervention considered on an individual basis.

Other neuropsychiatric events reported in clinical trials and during post-approval use included psychosis, paranoia, hallucinations, anxiety, irritability, hostility, aggression, and agitation. The emergence of thought disorders and/or behaviour abnormalities when patients are treated with sodium oxybate requires careful and immediate evaluation, including during dose titration.

Depression and Suicidality

In clinical trials, 6% of patients treated with sodium oxybate reported adverse events of depressive symptoms. In the majority of cases, no change in sodium oxybate treatment was required. Three patients (<1%) discontinued because of depressive symptoms. There was no dose relationship in depression reported during clinical trials.

Among patients with a previous history of depressive psychiatric disorder, there were two suicides and one attempted suicide recorded in the 448 patient dataset. Of the two suicides, one patient used multiple drugs, including sodium oxybate. Sodium oxybate was not involved in the second suicide. Sodium oxybate was the only drug involved in the attempted suicide. A fourth patient without a previous history of depression attempted suicide by taking an overdose of a drug other than sodium oxybate.

The emergence of depression when patients are treated with Xyrem requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/or suicide attempt should be monitored especially carefully for the emergence of depressive symptoms while taking Xyrem. Xyrem is not recommended in patients with major depression.

General

Incontinence

During clinical trials, 9% of narcoleptic patients treated with sodium oxybate experienced either a single episode or sporadic nocturnal urinary incontinence and <1% experienced a single episode of nocturnal fecal incontinence. Less than 1% of patients discontinued as a result of incontinence. Nocturnal urinary incontinence has been reported at all doses tested.

In a controlled clinical trial where patients were randomized to fixed total daily doses of 3, 6, and 9 g/night or placebo, a dose-response relationship for urinary incontinence was demonstrated with 14% of patients at 9 g/night experiencing urinary incontinence. In the same trial, one patient experienced fecal incontinence at a dose of 9 g/night and discontinued treatment as a result.

If a patient experiences urinary or fecal incontinence during Xyrem therapy, the prescriber should consider pursuing investigations to rule out underlying etiologies, including worsening sleep apnea or nocturnal seizures, although there is no evidence to suggest that incontinence has been associated with seizures in patients being treated with Xyrem.

Parasomnias

The term “sleepwalking” in this section refers to confused behaviour occurring at night and, at

times, associated with wandering. It is unclear if some or all of these episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Sleepwalking was reported in 7% of 448 patients treated in clinical trials with sodium oxybate. In sodium oxybate-treated patients <1% discontinued due to sleepwalking. In controlled trials of up to 4 weeks in duration, the incidence of sleepwalking was 1% in both placebo and sodium oxybate-treated patients. Sleepwalking was reported by 32% of patients treated with sodium oxybate for periods up to 16 years in one independent uncontrolled trial. Fewer than 1% of the patients discontinued due to sleepwalking. Five instances of significant injury or potential injury were associated with sleepwalking during a clinical trial of sodium oxybate over 16 years, including a fall, clothing set on fire while attempting to smoke, attempted ingestion of nail polish remover, and overdose of sodium oxybate. Sleep walking has also been reported during postmarketing experience with sodium oxybate. Therefore, episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

Sodium Intake

Each mL of Xyrem (sodium oxybate) oral solution contains 91 mg of sodium (refer to Table 1, below). Sodium content should be considered when prescribing Xyrem for patients with salt restrictions such as hypertension, congestive heart failure, or compromised renal function.

Table 1: Sodium Content per Total Nightly Xyrem Dose

Total Nightly Dose (g)	Total Nightly Dose (mL)	Sodium Content/ Total Nightly Dose
3	6	546 mg
4.5	9	819 mg
6	12	1092 mg
7.5	15	1365 mg
9	18	1638 mg

Dependence/Tolerance

Dependence

There have been case reports of dependence after illicit use of GHB at frequent repeated doses in excess of the therapeutic dose range (18 to 250 g/day). In these cases, the discontinuation resulted in an abstinence syndrome consisting of insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, and tachycardia, generally abating in 3 to 14 days. The effects of sodium oxybate discontinuation have not been systematically evaluated in controlled clinical trials. Neither a withdrawal nor an abstinence syndrome has been reported during clinical investigations, although, 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 markedly increased.

Tolerance

Tolerance to sodium oxybate has not been systematically studied in controlled clinical trials. Open-label, long-term (≥ 6 months) clinical trials did not demonstrate development of tolerance. There have been some case reports of symptoms of tolerance developing after illicit GHB use at dosages far in excess of the recommended Xyrem dosage regimen. Clinical studies of sodium oxybate in the treatment of alcohol withdrawal suggest a potential cross-tolerance with alcohol. 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 sodium oxybate (e.g., increase in size or frequency of dosing, drug-seeking behaviour). Physicians should document the diagnosis and indication for Xyrem, being alert to drug-seeking behaviour and/or feigned cataplexy.

Hepatic/Biliary/Pancreatic

Hepatic Insufficiency

Patients with compromised liver function will have an increased elimination half-life and systemic exposure to sodium oxybate (see ***Special Populations and Conditions*** in **ACTION AND CLINICAL PHARMACOLOGY**). Decrease the starting dose by one-half in such patients, and closely monitor the response to any dose increments (see **DOSAGE AND ADMINISTRATION**).

Psychiatric

Dependence Liability

Xyrem (sodium oxybate or gamma-hydroxybutyrate (GHB)), is classified as a Schedule III controlled substance by Federal law.

Drug Abuse

While sodium oxybate has not been systematically studied in clinical trials for its potential for abuse, illicit use and abuse of GHB have been reported. Sodium oxybate is a psychoactive drug that produces a wide range of pharmacological effects. It is a sedative-hypnotic that produces dose and concentration dependent central nervous system effects in humans. The onset of effect is rapid, enhancing its desirability as a drug of 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 (assault victim) user.

Illicit GHB has been abused in social settings primarily by young adults. Illicit GHB has some commonalties with ethanol over a limited dose range and some cross-tolerance with ethanol has been reported. Some of the doses reported during abuse may have been similar to the dose range studied for therapeutic treatment of cataplexy.

Renal

Renal Insufficiency

No studies have been conducted in patients with renal failure. Because less than 5% of sodium oxybate is excreted via the kidney, no dose adjustment should be necessary in patients with renal impairment. The sodium load associated with administration of sodium oxybate should be considered in patients with renal insufficiency.

Special Populations

Pregnant Women: Reproduction studies conducted in pregnant rats at doses up to 1000 mg/kg (approximately equal to the maximum recommended human daily dose on a mg/m2 basis) and in pregnant New Zealand White rabbits at doses up to 1200 mg/kg (approximately 3 times the maximum recommended human daily dose on a mg/m2 basis) revealed no evidence of teratogenicity. In a study in which rats were given sodium oxybate from Day 6 of gestation through Day 21 post-partum, slight increase in postnatal mortality and decreases in pup and maternal weight gains were seen at 1000 mg/kg; there were no drug effects on other developmental parameters.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Use in Obstetrics

Sodium oxybate has not been studied in labour 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. Therefore, use of Xyrem in obstetrics is not recommended unless clearly needed.

Nursing Women: Sodium oxybate is excreted in human milk. Caution should be exercised when Xyrem is administered to a nursing woman.

Pediatrics (< 18 years of age): The effects of sodium oxybate on early growth, development, and maturation in children are not known. The use of Xyrem is, therefore, not recommended in children under the age of 18, unless clearly needed.

Geriatrics (> 65 years of age): There is very limited experience with sodium oxybate in patients greater than 65 years of age. In general, dose selection in for elderly patients should start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concurrent disease or concomitant medications. Therefore, elderly patients should be monitored closely for impaired motor and/or cognitive function when taking Xyrem.

Monitoring and Laboratory Tests

Laboratory tests are not required to monitor patient response or adverse events resulting from Xyrem administration.

Information to Provide to the Patient

The Xyrem Patient Information section includes information about the safe and proper use of Xyrem, and information to help prevent accidental use or abuse of Xyrem by others. Physicians

and pharmacists should discuss the details of treatment with their patients, including the procedure for dose preparation, prior to the initiation of treatment. Patient educational materials are available, and patients should confirm that they have read and understood these materials. Patients should also be encouraged to read the Patient Package Insert for information regarding the proper use of Xyrem. Physicians should encourage their patients to be seen every 3 months during the course of Xyrem therapy and notify them that an account of the adverse reactions they may have experienced will be taken.

Specifically, the patient should be counselled on the following points:

- Xyrem has twice nightly dosing: the first dose is taken at bedtime and the second 2½ - 4 hours later.

- Xyrem is rapidly absorbed. Therefore, Xyrem should be taken only at bedtime, and patients should not walk around after taking their dose of Xyrem.

- The sudden onset of sleep, including in a standing position or while rising from bed, has led to falls complicated by injuries, and in some cases requiring hospitalization. Patients should remain in bed following ingestion of the first and second doses.

- Xyrem should not be taken with alcohol or other sedative hypnotics.

- Food significantly decreases the bioavailability of sodium oxybate. Whether Xyrem is taken in the fed or fasted state may affect both the efficacy and safety of Xyrem for a given patient. Patients should be made aware of this and take the first dose at least two hours after their last meal prior to bedtime.

- Xyrem may cause side effects including headache, dizziness, and nausea. Patients should also be made aware of the potential for enuresis and sleepwalking.

- Xyrem is a controlled substance. It is illegal to sell, distribute, or give Xyrem to anyone else, or to use Xyrem for purposes other than for what it was prescribed.

For additional information, see **PATIENT MEDICATION INFORMATION**.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

A total of 448 narcoleptic patients were exposed to sodium oxybate in clinical trials. The most commonly observed adverse events associated with the use of sodium oxybate were: Headache 25%, nausea 21%, dizziness 17%, pain (unspecified) 16%, somnolence 13%, pharyngitis 11%, infection 10%, viral infection 10%, flu syndrome 9%, accidental injury 9%, diarrhea 8%, urinary incontinence 8%, vomiting 8%, rhinitis 8%, asthenia 8%, sinusitis 7%, nervousness 7%, back pain 7%, confusion 7%, sleepwalking 7%, depression 6%, dyspepsia 6%, abdominal pain 6%, abnormal dreams 6%, and insomnia 5%.

Two deaths occurred in these clinical trials, both from intentional drug overdoses. Both of these deaths resulted from ingestion of multiple drugs, including sodium oxybate in one patient.

In these clinical trials, 13% of patients discontinued because of adverse events. The most frequent reasons for discontinuation (>1%) were nausea (2%) and headache (1%).

Approximately 6% of patients receiving sodium oxybate in 3 controlled clinical trials (n=147) withdrew due to an adverse event, compared to 1% receiving placebo (n=79). The reasons for discontinuation that occurred more frequently in sodium oxybate-treated patients than in placebo-treated patients were: nausea (3%), somnolence (2%) and confusion (1%). Amnesia, asthenia, chest pain, dizziness, dyspnea, fecal incontinence, hallucinations, headache, hyperkinesia, paranoid reaction, thinking abnormal, vertigo, and vomiting, caused discontinuation in a single patient each.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Incidence in Controlled Clinical Trials
Table 2 lists the most commonly reported adverse events from controlled clinical trials associated with the use of sodium oxybate.

Table 2: Most Common Adverse Events in Controlled Clinical Trials

Adverse Event COSTART Term	Placebo (n=79)	Sodium Oxybate (n=147)
Dizziness	3%	23%
Headache	15%	20%
Nausea	5%	16%
Somnolence	9%	12%
Pain (unspecified)	4%	12%
Sleep disorder	3%	9%
Confusion	1%	7%
Infection	1%	7%
Dyspepsia	6%	6%
Vomiting	1%	6%

Adverse Event COSTART Term	Placebo (n=79)	Sodium Oxybate (n=147)
Urinary incontinence	0%	5%
Nervousness	8%	5%

Table 3 lists the incidence of treatment emergent adverse events in Trial 1 (see **CLINICAL TRIALS**). Events have been included for which there are at least two episodes in the considered drug group and for which the incidence in at least one dosage group is greater on drug than placebo.

Table 3: Incidence (%) of Treatment-Emergent Adverse Events in Trial 1

Body System COSTART Term	Placebo (n=34)	Sodium Oxybate Dose 3 g (n=34)	6 g (n=33)	9 g (n=35)
Body as a Whole				
Asthenia	1 (3%)	0 (0%)	2 (6%)	0 (0%)
Flu Syndrome	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Headache	7 (21%)	3 (9%)	5 (15%)	11 (31%)
Infection	1 (3%)	3 (9%)	5 (15%)	0 (0%)
Infection Viral	1 (3%)	1 (3%)	3 (9%)	0 (0%)
Pain	2 (6%)	3 (9%)	4 (12%)	7 (20%)
Digestive System				
Diarrhea	0 (0%)	0 (0%)	2 (6%)	2 (6%)
Dyspepsia	2 (6%)	0 (0%)	3 (9%)	2 (6%)
Nausea	2 (6%)	2 (6%)	5 (15%)	12 (34%)
Nausea and Vomiting	0 (0%)	0 (0%)	2 (6%)	2 (6%)
Vomiting	0 (0%)	0 (0%)	2 (6%)	4 (11%)
Musculoskeletal System				
Myasthenia	0 (0%)	2 (6%)	1 (3%)	0 (0%)
Nervous System				
Amnesia	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Anxiety	1 (3%)	1 (3%)	0 (0%)	2 (6%)
Confusion	1 (3%)	3 (9%)	1 (3%)	5 (14%)
Dizziness	2 (6%)	8 (24%)	10 (30%)	12 (34%)
Dream Abnormal	0 (0%)	0 (0%)	3 (9%)	1 (3%)

Body System COSTART Term	Placebo (n=34)	Sodium Oxybate Dose 3 g (n=34)	 6 g (n=33)	 9 g (n=35)
Hypertension	1 (3%)	0 (0%)	2 (6%)	0 (0%)
Hypoesthesia	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Sleep Disorder	1 (3%)	2 (6%)	4 (12%)	5 (14%)
Somnolence	4 (12%)	5 (15%)	4 (12%)	5 (14%)
Thinking Abnormal	0 (0%)	1 (3%)	0 (0%)	2 (6%)
Skin				
Increased Sweating	0 (0%)	1 (3%)	1 (3%)	4 (11%)
Special Senses				
Amblyopia	1 (3%)	2 (6%)	0 (0%)	0 (0%)
Tinnitus	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Urogenital System				
Dysmenorrhea	1 (3%)	1 (3%)	0 (0%)	2 (6%)
Incontinence Urine	0 (0%)	0 (0%)	2 (6%)	5 (14%)

Other Adverse Events Observed During All Clinical Trials

During clinical trials sodium oxybate was administered to 448 patients with narcolepsy, and 125 healthy volunteers. A total of 150 patients received 9 g/night, the maximum recommended dose. A total of 223 patients received sodium oxybate for at least one year. To establish the rate of adverse events, data from all subjects receiving any dose of sodium oxybate were pooled. All adverse events reported by at least two people are included except for those already listed elsewhere in the labeling, terms too general to be informative, or events unlikely to be drug induced. These events are not necessarily related to sodium oxybate treatment.

Body As A Whole: >1%: Allergic reaction, chills; 1% - 0.1%: Abdomen enlarged, hangover effect, neck rigidity.

Cardiovascular system: 1% - 0.1%: Syncope.

Digestive system: >1%: Anorexia, constipation; 1% - 0.1%: Mouth ulceration, stomatitis.

Hemic and lymphatic system: 1% - 0.1%: Anemia, ecchymosis, leukocytosis, lymphadenopathy, polycythemia.

Metabolic and nutritional: >1%: Alkaline phosphatase increased, edema, hypercholesterolemia, hypocalcemia, weight gain; 1% - 0.1%: Bilirubinemia, creatinine increased, dehydration, hyperglycemia, hypernatremia, hyperuricemia, SGOT increased, SGPT increased, thirst.

Musculoskeletal system: >1%: Arthritis, leg cramps, myalgia.

Nervous system: >1%: Agitation, ataxia, convulsion, stupor, tremor; 1% - 0.1%: Akathisia, apathy, coma, depersonalization, euphoria, hypertonia, libido decreased, myoclonus, neuralgia, paralysis.

Respiratory system: >1%: Dyspnea; 1% - 0.1%: Apnea, epistaxis, hiccup.

Skin and appendages: >1%: Acne, alopecia, rash; 1% - 0.1%: Contact dermatitis, urticaria.

Special senses: 1% - 0.1%: Taste loss.

Urogenital system: >1%: Albuminuria, cystitis, hematuria, metrorrhagia, urinary frequency; 1% - 0.1%: Urinary urgency.

Post-Market Adverse Drug Reactions

In addition to the adverse drug reactions reported during clinical studies and listed above, the following adverse events have been identified during post-approval use of XYREM (sodium oxybate) oral solution. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure. Events that have been reported during post-marketing experience include: aggression, angioedema, arthralgia, decrease appetite, dry mouth, fall, fatigue, fluid retention, hypersensitivity, increased libido, memory impairment, nightmare, nocturia, panic attack, vision blurred, and weight loss.

United States Post-Marketing Experience

Between the period of July 2002 through September 30, 2004, a total of 5,869 patients have received Xyrem. Of those patients, 853 have discontinued Xyrem therapy, due to a wide range of reasons. Table 4 summarizes the most commonly reported adverse events (≥20 occurrences) during this time period. These adverse events are consistent with those identified in clinical studies.

Table 4: Summary of Post-Market Common Adverse Event Reports

System Organ Class, MedDRA preferred term	Number of Reports
Gastrointestinal Disorders	
Nausea	76
Vomiting	40
General Disorders and Administration Site Conditions	
Feeling abnormal	27
Nervous System Disorders	
Headache	40
Dizziness	28
Somnolence	33
Tremor	22
Psychiatric Disorders	

System Organ Class, MedDRA preferred term	Number of Reports
Confusion/confusional	47
Insomnia	43
Depression	22
Anxiety	21
Renal and Urinary Disorders	
Enuresis/incontinence	30

A U.S. Post-Marketing Evaluation Program (PMEP) was designed to capture solicited safety data on 1,000 additional patients receiving Xyrem therapy. The PMEP specifically queried for the adverse events, vomiting, incontinence, sleepwalking, confusion, and convulsions. Through September 30, 2004, a total of 695 PMEP reports had been received. No adverse event was reported in 467 of these reports. The number of reports received for the adverse events listed above is as follows: vomiting (17/695), incontinence (24/695), sleepwalking (9/695), confusion (28/695), and convulsions (1/695).

DRUG INTERACTIONS

Overview

Interactions between sodium oxybate and three drugs commonly used in patients with narcolepsy (zolpidem tartrate, protriptyline hydrochloride, and modafinil) have been evaluated in formal studies in healthy adults. Drug-drug interaction studies in healthy adults (18 to 50 years of age) were also conducted with sodium oxybate and divalproex sodium, diclofenac and ibuprofen.

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 µg/mL), a concentration that is considerably higher than the concentrations achieved with therapeutic doses.

In animal models, sodium oxybate and depressant drug combinations generally gave greater central depressant effects than did either drug alone. Concomitant administration to animals of sodium oxybate and benzodiazepines, barbiturates, or ethanol increases sleep duration. In primates, sodium oxybate blood levels were elevated with phenytoin pretreatment and reduced with L-Dopa, ethosuximide, and trimethadione.

Drug-Drug Interactions

Drug-drug interaction studies in healthy adults were conducted with sodium oxybate and protriptyline hydrochloride, zolpidem tartrate, modafinil, divalproex sodium, diclofenac or ibuprofen.

<u>Protriptyline hydrochloride, zolpidem tartrate, modafinil</u>

Sodium oxybate in combination with protriptyline hydrochloride, zolpidem tartrate, or modafinil produced no significant pharmacokinetic changes for sodium oxybate or the other drugs but, pharmacodynamic interactions cannot be excluded. Nonetheless, sodium oxybate should not be

used in combination with sedative hypnotics or other CNS depressants, including alcohol (see **CONTRAINDICATIONS; Serious Warnings and Precautions**).

Divalproex sodium
Co-administration of Xyrem (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 by approximately 25% as shown by AUC (AUC ratio range of 0.8 to 1.7), while Cmax 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. An initial dose reduction of at least 20% is recommended if divalproex sodium is prescribed to patients already taking Xyrem (see **DOSAGE AND ADMINISTRATION**). Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of Xyrem and divalproex sodium is warranted.

Diclofenac
Co-administration of Xyrem (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 Xyrem (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 Cmax and AUC values. Co-administration did not appear to affect the pharmacokinetics of ibuprofen.

Drug-Food Interactions
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 Tmax increased from 0.75 hr to 2.0 hr) and a reduction in peak plasma level (Cmax) by a mean of 58% and of systemic exposure (AUC) by 37%.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Xyrem should only be prescribed by physicians who meet the following requirements: i) Experience in treating cataplexy in patients with narcolepsy; ii) Completion of the Xyrem Physician Success Program.

The Xyrem Success Program is a Risk Management Program founded on the following core components that provide for the safe and effective use of the drug, and limit the potential for drug diversion and abuse:

i) Implementation of a program to educate physicians, pharmacists, and patients

about the risks and benefits of XYREM, including critical information necessary for the safe use, storage, and handling of the drug.

ii) **Implementation of a restricted distribution program for Xyrem through a single wholesale distribution company that will ship the drug directly to pharmacies on an as-needed basis after patients have presented with an initial legitimate prescription.**

iii) **Filling of the initial prescription only after the prescriber, pharmacist, and patient have received and read the educational materials.**

iv) **Maintenance of a registry of Xyrem Success Program trained physicians, pharmacies, and patients.**

Xyrem is not recommended for use in other indications as safety and efficacy have not been established outside of cataplexy.

Physicians may obtain more information about the Xyrem Success Program by calling the following toll-free phone number: 1-866-5XYREM5 (1-866-599-7365).

Recommended Dose and Dosage Adjustment

Xyrem (sodium oxybate) should be titrated to effect. The recommended starting dose is 4.5 g/night divided into two equal doses of 2.25 grams. The first dose should be taken at bedtime, and the second dose should be taken 2.5 to 4 hours later. The starting dosage can be increased or decreased in increments of 1.5 g/night (0.75 g per dose) to a maximum of 9 g/night while evaluating clinical response and adverse effects. Two-week intervals are recommended between dose titration. Xyrem is effective at doses of 6 to 9 g/night. The efficacy and safety of Xyrem at doses higher than 9 g/night have not been investigated, and doses greater than 9 g/night are not recommended. Eight to 10 weeks of therapy may be necessary before a maximal cataplexy response to sodium oxybate is seen (see Clinical Experience below).

Xyrem is an oral solution with a concentration of 500 mg/mL sodium oxybate. Table 5 provides a conversion scale of total nightly Xyrem dose(s) from grams to mL.

Table 5: Total Nightly Dose: Conversion Scale

Total Nightly Dose (g)	Total Nightly Dose (mL)	Single Dose (taken twice nightly) (g)	Single Dose (taken twice nightly) (mL)
3 g	6 mL	1.5 g	3 mL
4.5 g	9 mL	2.25 g	4.5 mL
6 g	12 mL	3 g	6 mL
7.5 g	15 mL	3.75 g	7.5 mL
9 g	18 mL	4.5 g	9 mL

Because food significantly reduces the bioavailability of sodium oxybate, the patient should try

to eat at least two hours before going to sleep and taking the first dose of Xyrem. Patients should try to minimize variability in the timing of dosing in relation to meals.

Clinical Experience

In Trial 3, an open-label trial, 117 patients with narcolepsy entered at a sodium oxybate starting dose of 6 g/night (3 g twice per night) and were titrated to optimum clinical response between the doses of 3 and 9 g/night. The nadir in cataplexy occurred 8 to 10 weeks later. This response was maintained across the remainder of the treatment period in general without dose escalation (U.S. Xyrem Multicenter Study Group 2003). Maintained treatment and appropriate dose titration is important for clinical response. In approximately 77% (90/117) of patients, maintenance doses were between 6 to 9 g/night.

Trial 4 was an open-label trial in 185 patients with narcolepsy in which sodium oxybate was added to existing treatments. Patients were entered at a starting dose of 4.5 g/night (2.25 g twice per night) followed by dose titration in 1.5 g increments over two week periods to optimize clinical response. Anti-depressant medications were then down-titrated. Seventy-two percent (31/43) of patients taking tricyclic antidepressants and 53% (19/36) of patients taking selective serotonin reuptake inhibitors for cataplexy reduced or discontinued use of these concomitant medications. In general, sodium oxybate dosing remained unchanged, with only 9 of these patients requiring an increase in dosage following discontinuation of prior medications.

Hepatic Insufficiency

Patients with compromised liver function will have a longer elimination half-life and greater systemic exposure along with reduced clearance. (See ***Special Populations and Conditions*** in **ACTION AND CLINICAL PHARMACOLOGY** and **Hepatic/Biliary/Pancreatic** in **WARNINGS AND PRECAUTIONS**). As a result, the starting dose should be decreased by one-half and dose increments should be titrated to effect while closely monitoring potential adverse events.

Dose Adjustment with Co-administration of Divalproex Sodium

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

Administration

Preparation and Administration

Prepare both doses of Xyrem prior to bedtime. Each dose of Xyrem must be diluted with approximately 60 mL (2 oz) of water or enough to fill ¾ of the supplied dosing cups provided prior to ingestion and sealed with the child-resistant cap. The first dose is to be taken at bedtime, and the second dose is to be taken 2.5 to 4 hours later while sitting in bed. Patients may need to set an alarm to awaken for the second dose. The second dose must be prepared prior to ingesting the first dose, and should be placed in close proximity to the patient's bed. After ingesting each

dose, the patient should lie down and remain in bed.

Each bottle of Xyrem is provided with a child-resistant cap and two dosing cups with child-resistant caps.

See **PATIENT MEDICATION INFORMATION** for a complete description.

OVERDOSAGE

Signs and Symptoms

Information regarding overdose with sodium oxybate is extrapolated from literature reports of toxicity from illicit GHB. The co-ingestion of other drugs and alcohol is common, and may influence the presentation and severity of clinical manifestations of overdose. Therefore, literature reports of GHB overdose must be interpreted cautiously because overdose may be indistinguishable from other drug overdoses or medical conditions.

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 may be 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.

In clinical trials, two cases of overdose with Xyrem (sodium oxybate) oral solution 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 experience urinary and fecal incontinence. This individual recovered without sequelae. In the second case, death was reported following a multiple drug overdose consisting of Xyrem and numerous other drugs.

Recommended Management

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) or 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 intravenous atropine 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.

As with the management of all cases of drug overdosage, the possibility of multiple drug ingestion should be considered. The physician is encouraged to collect urine and blood samples for routine toxicologic screening, and to consult with a regional poison control center for current treatment recommendations.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism by which sodium oxybate (also known as gamma-hydroxybutyrate; GHB) produces its anti-cataplectic effects is unknown. Gamma hydroxybutyrate is a CNS depressant that produces dose-dependent sedation and anesthesia. GHB is also an endogenous compound that is widely found throughout the body although its function outside of the CNS is essentially unknown. Endogenous GHB appears to fulfill the criteria necessary to be considered a neurotransmitter or neuromodulator.

Pharmacodynamics

The pharmacodynamic response to sodium oxybate dosing (4.5 to 9 g/night) in terms of sleep architecture was characterized in 21 patients with narcolepsy. A dose-related increase in Stages 3 and 4 (slow-wave) sleep and delta power was noted, with improved sleep continuity represented by a dose-related decrease in the number of nighttime awakenings, without significant changes in total sleep time. Also noted were dose related decreases in total REM sleep and a decrease in Stage 1 sleep. No significant changes were seen in Stage 2 sleep nor the duration of wake after sleep onset. Measurement of daytime wakefulness utilizing the Maintenance of Wakefulness Test showed dose related increases in sleep latency and a dose related decrease in the percentage of patients with sleep-onset REM periods. A dose related decrease in the Epworth Sleepiness Score was also seen.

Pharmacokinetics

Sodium oxybate is rapidly but incompletely absorbed after oral administration; absorption is delayed and decreased by a high fat meal. It is eliminated mainly by metabolism with a half-life of 0.5 to 1 hour. Pharmacokinetics are non-linear with blood levels increasing 3.7-fold as dose is doubled from 4.5 to 9 grams (g). The pharmacokinetics are not altered with repeat dosing.

Absorption: Sodium oxybate is absorbed rapidly following oral administration with an absolute bioavailability of about 88%. The average peak plasma concentrations (1st and 2nd peak) following administration of a 9 g daily dose divided into two equivalent doses given four hours apart were 78 and 142 µg/mL, respectively. The average time to peak plasma concentration (Tmax) ranged from 0.5 to 1.25 hours in eight pharmacokinetic studies. Following oral

administration, the plasma levels of sodium oxybate increased more than proportionally with increasing dose.

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 Tmax increased from 0.75 hr to 2.0 hr) and a reduction in peak plasma level (Cmax) by a mean of 58% and of systemic exposure (AUC) by 37%.

Distribution: Sodium oxybate is a hydrophilic compound with an apparent volume of distribution averaging 190 to 384 mL/kg. At sodium oxybate concentrations ranging from 3 to 300 µg/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 catalyses 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 catalyses 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.

Excretion: 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.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of sodium oxybate in patients under the age of 18 years have not been studied.

Geriatrics: The pharmacokinetics of sodium oxybate in patients greater than the age of 65 years 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 following a single oral dose of 4.5 g.

The overall clinical trial database was 58% female. No important differences in safety or efficacy of Xyrem were noted between men and women. The overall percentage of patients with at least one adverse event was higher in women (80%) than in men (69%). The incidence of serious adverse events and discontinuations due to adverse events were similar in both men and women.

Race: There were too few non-Caucasian subjects in clinical trials to evaluate the effects of race on pharmacokinetics, safety or efficacy. More than 90% of the subjects in clinical trials were Caucasian.

Hepatic Insufficiency: Sodium oxybate undergoes significant presystemic (hepatic first-pass) metabolism. 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 pharmacokinetics in 8 healthy adults 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 subjects (mean t½ of 59 and 32 versus 22 minutes). It is prudent to reduce the starting dose of Xyrem by one-half in patients with liver impairment (see **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency: Because the kidney does not have a significant role in the excretion of sodium oxybate, no pharmacokinetic study in patients with renal impairment has been conducted; no effect of renal function on sodium oxybate pharmacokinetics would be expected. The sodium load associated with the administration of sodium oxybate should be considered in patients with renal insufficiency.

STORAGE AND STABILITY

Store between 15°-30°C.
Following dilution, solutions prepared should be consumed within 24 hours to minimize bacterial growth and contamination.

SPECIAL HANDLING INSTRUCTIONS

Any unused Xyrem should be returned to the pharmacy for proper disposal. Do not pour it down the drain.

Care should be taken to prevent access to this medication by children and pets.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Xyrem (sodium oxybate) oral solution contains 500 mg of sodium oxybate per millilitre of USP purified water, neutralized to pH 7.5 with malic acid.

Xyrem (sodium oxybate) is a clear to slightly opalescent oral solution. It is supplied in a tamper evident single unit carton containing one bottle of Xyrem, a press-in-bottle-adapter (PIBA), a 10 mL oral measuring device (plastic syringe), and a Patient Package Insert. Each amber oval PET bottle contains 180 mL of Xyrem oral solution at a concentration of 500 mg/mL and is sealed with a child-resistant cap. The pharmacist places the PIBA in the bottle prior to dispensing Xyrem to the patient along with two 90 mL dosing cups with child-resistant caps.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

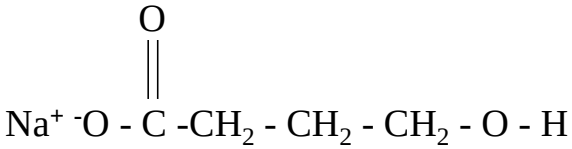
Drug Substance

Proper name: Sodium oxybate

Chemical name: Sodium 4-hydroxybutyrate

Molecular formula and molecular mass: $C_4H_7NaO_3$, 126.09 grams/mole

Structural formula:



Physicochemical properties:

Description: Sodium oxybate is a white to off-white, crystalline powder.
Solubilities: Freely soluble in water. Insoluble in acetone and ethanol.
Melting point: 146°-149°C (after drying at 105°C for 45 min.)

CLINICAL TRIALS

Study demographics and trial design

The effectiveness of sodium oxybate as an anti-cataplectic agent was established in two randomized, double-blind, placebo-controlled trials (Trials 1 and 2) in patients with narcolepsy, 85% and 80%, respectively, of whom were also being treated with CNS stimulants. The high percentages of concomitant stimulant use make it impossible to assess the efficacy and safety of Xyrem independent of stimulant use. In each trial, the treatment period was 4 weeks and the total daily doses ranged from 3 to 9 g, with the daily dose divided into 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 1 was a multi-center, double-blind, placebo-controlled, parallel-group trial that 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/night, sodium oxybate 6 g/night, or sodium oxybate 9 g/night.

Trial 2 was a multi-center, double-blind, placebo-controlled, parallel-group, randomized withdrawal trial that enrolled 55 narcoleptic patients who had been taking open-label sodium oxybate for 7 to 44 months. 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 or to placebo. Trial 2 was designed specifically to evaluate the continued efficacy of sodium oxybate after long-term use.

The primary efficacy measure in each clinical trial was the frequency of cataplexy attacks.

Table 6
Summary of Outcomes in Clinical Trials Supporting
the Efficacy of Sodium Oxybate

Trial/ Dosage Group g/night (n)	Baseline	Median Change From Baseline	Comparison to Placebo p-value
CATAPLEXY ATTACKS			
Trial 1			
		(median attacks/week)	
Placebo (33)	20.5	-4	—
3.0 (33)	20.0	-7	0.5541
6.0 (31)	23.0	-10	0.0451
9.0 (33)	23.5	-16	0.0016
Trial 2			
		(median attacks/two weeks)	
Placebo (29)	4.0	21.0	-
Sodium oxybate (26)	1.9	0	<0.001

In Trial 1, both the 6 g/night and 9 g/night doses gave statistically significant reductions in the frequency of cataplexy attacks. The 3 g/night dose had little effect. In Trial 2, following the discontinuation of long-term open-label sodium oxybate therapy, patients randomized to placebo experienced a significant increase in cataplexy ($p<0.001$), providing evidence of long-term efficacy of sodium oxybate. In Trial 2, the response was numerically similar for patients treated with doses of 6 to 9 g/night, but there was no effect seen in patients treated with doses less than 6 g/night, suggesting little effect at these doses.

Results from two open-label trials (Trial 3 and Trial 4) provide further information regarding dosing of sodium oxybate (see Clinical Experience**, DOSAGE AND ADMINISTRATION**).

DETAILED PHARMACOLOGY

Animal Studies

The precise mechanism of action of sodium oxybate is not known even though many studies of its pharmacology have been performed. Gamma-hydroxybutyrate (GHB) produces dose-dependent sedation and anesthesia in laboratory animals. It is active when given orally or by IV or IP injection. GHB-induced sleep has most often been assessed on a behavioural level in animals by its ability to induce loss of the righting reflex. This has been demonstrated in a number of rodent and non-rodent species. Brain levels of GHB associated with loss of the

righting reflex after its systemic administration are 500 to 1000 times those found endogenously. GHB has a rapid onset and short duration of action, depending on dose and route of administration.

Endogenous GHB satisfies criteria as a neuromodulator or neurotransmitter in the central nervous system. GHB is a unique pharmacological entity that functions as a neuromodulator distinct from GABA or GABAergic compounds. GHB binds reversibly, selectively and with high affinity to two different receptor sites for GHB that show a heterogeneous distribution in the central nervous system different from that of GABA receptors. Activation of GHB receptors results in alterations in second messenger systems, including elevated cGMP levels, inositol phosphate turnover, and nitric oxide synthesis.

GHB can influence the activity of GABA as well as other amino acids (glutamate, glycine) in the brain by affecting their levels and/or release. GHB also influences the dopaminergic system. Doses of GHB that induce loss of righting also increase brain dopamine levels. Although GHB does not appear to directly influence dopamine synthesis or degradation, it can influence the firing of dopaminergic neurons, the release of dopamine, and the expression of dopamine D1 and D2 receptors. A GHB receptor-mediated influence on endogenous opioid peptides has been demonstrated. There appears to be less influence of GHB on serotonergic, noradrenergic, and cholinergic systems.

In studies in rodents and primates, sodium oxybate did not show effects in common with abused stimulant or depressant drugs, including benzodiazepines, barbiturates, heroin, morphine, cocaine, d-amphetamine, phencyclidine, and LSD. There were some commonalties with ethanol over a limited dose range and some cross-tolerance with ethanol has been reported. Self-administration studies of oxybate in monkeys fail to show evidence of strong reinforcing effects but some studies in rodents demonstrate weak reinforcing properties.

TOXICOLOGY

Acute Toxicity

The acute toxicity of GHB has been studied in mice, rats, rabbits, and dogs primarily by parenteral routes of administration. Reported lethality (from respiratory depression) ranges from an LD50 IP of 1700 mg/kg up to 9990 mg/kg orally in the rat.

Long-Term Toxicity

In a 90-day study in rats, there were no toxicological effects attributed to sodium oxybate at a dose of 350 mg/kg/day (2.7 times the maximum recommended daily human dose). At the high dose of 1000 mg/kg/day, treatment-related effects included transient post-dose hypoactivity and prostration, and decreased body weight, body weight gain and food consumption. There were no histopathological changes seen in any tissue.

Twenty-six week oral treatment in rats again produced hypoactivity, decreased body weight, and decreased food consumption at the high dose of 1000 mg/kg/day. No changes in the other parameters (gross pathology, organ weights, microscopic pathology) were reported. The no-

effect dose was 350 mg/kg/day (2.7 times the maximum human dose).

In the 90-day study in dogs, emesis was seen as the dose limiting effect. At 350 mg/kg/day, the incidence of emesis was low and this dose was considered to be a no-adverse-effect level (NOAEL). Histopathological evaluation of tissues revealed atrophy of the mandibular salivary glands and submucosal glands of the esophagus at 600 mg/kg/day.

In a 52-week study in dogs, initial doses were 150, 350, and 600 mg/kg/day; however, the high dose was subsequently raised to 900 mg/kg/day during Week 32. Clinical signs (emesis, soft feces, tremors, thin appearance, hypoactivity, ataxia, salivation, prostration) were reported at 350 and 600/900 mg/kg/day. Body weight loss and decreased weight gain occurred in the high-dose animals. The only other effect was atrophy of the mandibular salivary glands and the submucosal mucous glands of the esophagus at 350 and 600 mg/kg/day. No gender differences or changes due to repeated dosing were observed. The no-effect level in this study was 150 mg/kg/day (1.2 times the maximum human dose).

Carcinogenicity
Oral carcinogenicity studies have been conducted in rats and mice with gamma-butyrolactone, a compound that is metabolized to sodium oxybate in vivo, with no clear evidence of carcinogenic potential. Plasma levels (AUC) of sodium oxybate achieved in these studies were estimated to be approximately 1/2 (mice and female rats) and 1/10 (male rats) those seen in humans receiving the maximum recommended daily dose of sodium oxybate.

A sponsor-initiated, two-year rat carcinogenicity study compared daily oral (gavage) sodium oxybate dosages of 0, 200, 500 and 1000 mg/kg. Decreased survival of males at 1000 mg/kg/day during the second half of the second year of the study resulted in discontinuance of test article administration in this sex group beginning in Week 83 of the study. No test article-related organ weight or macroscopic and microscopic pathology changes were observed. No oncogenic effect was observed.

Mutagenicity
Sodium oxybate was negative in three mutagenicity assays: the Ames test, the in vitro chromosomal aberration assay, and the in vivo rat micronucleus assay.

Reproductive Toxicity
A Segment I fertility study was conducted in rats at doses of 150, 350, and 1000 mg/kg/day from 28 days (males) and 14 days (females) prior to mating. Females were treated through Day 7 of gestation. An effect on the overall reproductive performance was not observed in this study.

Segment II teratology studies, indicated that sodium oxybate was not teratogenic. In rats and rabbits no developmental toxicity was reported at dosages to 1000 and 1200 mg/kg/day, respectively.

In a Segment III study of perinatal and postnatal effects, sodium oxybate was administered to pregnant rats at doses of 150, 350, and 1000 mg/kg/day from Day 6 of gestation through Day 20 of lactation. Pregnancy, implantation sites, and live birth indices were unaffected by treatment at

any dose. There was an increase in postnatal mortality at 1000 mg/kg/day, and surviving pups showed lower rates of growth. Post-weaning behavioural and maturational assessments, including fertility, showed no drug-related effects. The no-effect dose in this study was 350 mg/kg/day.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

Xyrem® (ZIE-rem)
(sodium oxybate) oral solution 500 mg/mL

Read this carefully before you start taking **Xyrem®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Xyrem®**.

It is very important that you carefully read and follow all instructions before using Xyrem. You are encouraged to read this leaflet again before each refill as there may be new information. This information does not take the place of talking with your doctor or pharmacist about your medical condition or your treatment. Your doctor should instruct you in the safe and effective use of Xyrem. If you have any questions about Xyrem, ask your doctor or pharmacist. Do not throw away this Patient Package Insert or any other information on Xyrem that your doctor or pharmacist have provided. You may need to refer to the information again later.

What is the most important information I should know about Xyrem?

- The Xyrem Success Program, developed by the manufacturer of Xyrem, includes recommendations to doctors and pharmacists for educating patients on the safe and proper use of Xyrem. Through the Xyrem Success Program, educational materials will be provided to you by your doctor or pharmacist. Your doctor should confirm with you that you have read and understood these materials. During the course of Xyrem therapy, you should be seen by your doctor every 3 months, and an account of any side effects you may have experienced should be taken.
- Xyrem is available only by prescription and is a federally controlled drug. This means that it is illegal for you to sell, distribute, or give your Xyrem to anyone else, or for you to use your Xyrem for purposes other than for what it was prescribed.
- It is critical to keep Xyrem out of the reach of children.
- Xyrem may cause you to fall asleep quickly. Therefore, take Xyrem only at bedtime and while in bed. Do not drive a car, operate heavy machinery, or perform any activity that requires mental alertness for at least 6 hours after taking Xyrem, until you know whether it makes you sleepy the next day.
- The active ingredient in Xyrem is gamma-hydroxybutyrate (GHB), a chemical that has been abused (misused). Abuse can cause serious medical problems, including trouble breathing, seizures (convulsions), loss of consciousness, coma, and death. Abuse of Xyrem could also lead to dependence, craving for the medicine, and severe withdrawal symptoms.

What is Xyrem used for?
Xyrem is a brand of medicine used to reduce the number of cataplexy (weak or paralyzed muscles) attacks in patients with narcolepsy.

How does Xyrem work?
The mechanism by which Xyrem produces its anti-cataplectic effects is unknown.

What are the ingredients in Xyrem?
Medicinal ingredients: Sodium oxybate
Non-medicinal ingredients: Purified water and malic acid.

Xyrem comes in the following dosage forms:
Oral solution containing 500 mg/mL sodium oxybate.

Do not use Xyrem if you:

- take other sleep medicines or sedatives (medicines that cause sleepiness).
- have a rare condition called succinic semialdehyde dehydrogenase deficiency.
- are allergic to Xyrem or any of its ingredients.

Do not drink alcohol while you are taking Xyrem.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Xyrem. Talk about any health conditions or problems you may have, including if you:

- have had depression. You may be more likely to get depressed taking Xyrem.
- have liver problems. Your dose may need to be adjusted.
- have sleep apnea, snoring, or breathing or lung problems. You may be more likely to get serious side effects.
- are on a salt restricted diet, have high blood pressure, or heart failure. Xyrem contains significant levels of sodium (salt) and may not be right for you.
- are pregnant or plan to become pregnant or are breastfeeding. Xyrem can pass through your milk and may harm the baby.

Tell your doctor or pharmacist about all the medicines you take, including prescription and non-prescription medicines, and natural health products.

Other w**arnings you should know about:**
Do not drink alcohol or take sedatives. Alcohol and certain medicines can increase the chance of dangerous side effects, such as difficulty breathing, extreme sleepiness, low blood pressure, and loss of consciousness.

Do not drive a car, operate heavy machinery, or perform any activity that requires mental alertness for at least 6 hours after taking Xyrem. When you first start taking Xyrem, use extreme care while undertaking similar activities the next day.

You should remain in bed after you have taken the first and second dose of Xyrem. Do not take the second dose until 2½ to 4 hours after the first dose. Xyrem can cause you to fall asleep quickly. Falling asleep while standing or while rising from the bed has led to falls and injuries which, in some cases, required hospitalization.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Xyrem:

- alcohol or other sedative hypnotics
- antiepileptic drugs such as divalproex sodium (valproic acid) and topiramate

How to take Xyrem:

- It is important that you take Xyrem exactly as prescribed by your doctor.
- You and your physician will discuss your response to treatment including any side effects you may be experiencing, and your physician may adjust your dose as a result. **Never change the dose of Xyrem yourself**.
- Take Xyrem two times each night. Take the first dose right at bedtime and the second dose 2 ½ to 4 hours later. You may need to set an alarm to make sure you wake up to take the second dose
- You have to prepare the doses before you take them. You must mix each prescribed dose with 60 mL of water (2 ounces). See "**How to Prepare and Take the Nightly Doses of Xyrem**" for detailed instructions.
- Food will decrease the amount of Xyrem that your body absorbs. Make sure you eat your last meal at least 2 hours before you go to bed.
- Xyrem has a sedative effect and can make you sleepy. Stay in bed after you have taken the first and second doses of Xyrem.

Usual dose:

- The starting dose is usually 4.5 grams total per night, divided in two equal doses of 2.25 grams each.
- Based on how you feel, your doctor may increase or decrease the dose every two weeks.
- The usual dose is between 6 grams to 9 grams in total per night.
- You can expect to see some improvement within the first weeks of Xyrem therapy. It may take up to 8 to 10 weeks to have the full benefits of Xyrem.

How to Prepare and Take the Nightly Doses of Xyrem:

CAUTION: Be very careful not to leave your Xyrem in a place where children or pets can get to it.

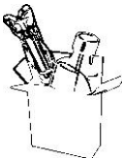
The Xyrem carton contains:

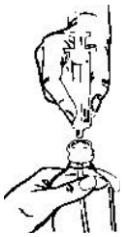
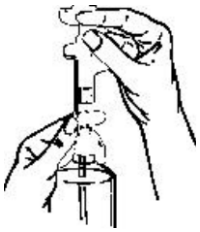
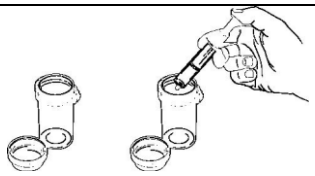
- 1 bottle of medicine
- printed product information
- 2 dosing cups with child-resistant caps
- 1 liquid measuring device (an oral syringe)

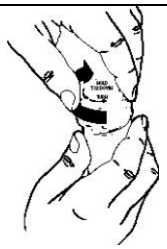
The measuring device is an oral syringe with markings only in grams. In case you need the dose in millilitres (mL), you can consult the conversion tables below:

Single dose in grams (to be taken twice per night)	**Single dose in mL** (to be taken twice per night)
1.5 grams	3 mL
2.25 grams	4.5 mL
3 grams	6 mL
3.75 grams	7.5 mL
4.5 grams	9 mL

Total dose per night in grams	**Total dose per night in mL**
3 grams	6 mL
4.5 grams	9 mL
6 grams	12 mL
7.5 grams	15 mL
9 grams	18 mL

Step 1 Remove the Xyrem bottle and the measuring device from the box (See Figure 1).	 Figure 1

Step 2 Remove the measuring device from the wrapper (See Figure 2).	 Figure 2
Step 3 Remove the bottle cap by pushing down while turning the cap counterclockwise (to the left). (See Figure 3). After removing the cap, set the bottle upright on a tabletop.	 Figure 3
Step 4 While holding the bottle in its upright position, insert the tip of the measuring device into the centre opening on top of the bottle and press down firmly (See Figure 4).	 Figure 4
Step 5 While holding the bottle and measuring device down with one hand, draw up the prescribed dose with the other hand by pulling on the plunger. **Notes:** • Xyrem is a liquid and your individual prescription contains a description of your dose in grams (g) of Xyrem. Use the markings in grams on the oral syringe to determine your prescribed dose. • Medicine will not flow into the measuring device unless you keep the bottle in its upright position (See Figure 5).	 Figure 5
Step 6 Remove the measuring device (oral syringe) from the centre opening of the bottle. Empty the medicine from the measuring device into one of the dosing cups provided by pushing on the plunger. Then add in approximately 60 mL or 2 ounces (oz) of water (or enough to fill ¾ of the cup). Repeat the process with the second dosing cup (See Figure 6).	 Figure 6

Step 6 (continued) **Prepare both doses just before bedtime.** Place the caps provided on the dosing cups and turn each cap clockwise (to the right) until it clicks and locks into its child-resistant position (See Figure 7). Recap the Xyrem bottle and store it in a safe and secure place (locked up if appropriate), out of the reach and sight of children and pets. Rinse out the liquid measuring device with water.	 Figure 7
Step 7 Right before going to sleep, place your second dose in a secure location (locked up if appropriate) near your bed. You may need to set an alarm so you wake up to take your second dose no earlier than 2 ½ hours and no later than 4 hours after your first dose. Remove the cap from the first dosing cup by pressing down on the child-resistant locking cap (See Figure 8) and turning the cap counterclockwise (to the left). Drink the entire first dose while sitting in bed, recap the cup, and then lie down right away (See Figure 9).	 Figure 8  Figure 9
Step 8 When you wake up 2½ to 4 hours later, remove the cap from the second dosing cup. While sitting in bed, drink the entire second dose; recap the second cup and then lie down to continue sleeping.	

Overdose:

- For the management of a suspected drug overdose, consult your regional Poison Control Centre.
- If you take more Xyrem than prescribed or take it by accident, seek medical help.

If you think you have taken too much Xyrem, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss the second dose, skip that dose and do not take Xyrem again until the next night. Never take two Xyrem doses at once.

What are possible side effects from using Xyrem?

These are not all the possible side effects you may feel when taking Xyrem. If you experience any side effects not listed here, contact your healthcare professional. Please also see **Warnings you should know about**.

- The most common side effects of Xyrem are headache, nausea, dizziness, sleep problems, confusion, vomiting, and frequent urination. Some patients may experience infrequent bed-wetting during the night. To help prevent bed-wetting, make sure you go to the bathroom before taking your first dose of Xyrem.

These are not all of the side effects of Xyrem. If you are concerned about any possible side effects consult your

doctor or pharmacist.

Effects of abusing (misusing) Xyrem (GHB)

- GHB (gamma-hydroxybutyrate) can be a drug of abuse if used improperly, and some people who repeatedly abuse GHB become addicted to it. People who repeatedly abuse GHB at high frequency and at high doses can develop withdrawal symptoms. These symptoms include the need to continue taking the drug, anxiety, trouble sleeping, and abnormal thinking.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON Increases sleepiness during the day	✓		
UNCOMMON Confusion		✓	
Aggression		✓	
Sleepwalking: walk while being asleep			✓
Depression			✓
Seizure			✓
Abnormal thinking			✓
Breathing problems			✓
Sleep apnea: stop breathing while you sleep			✓
UNKNOWN Hallucination: seeing or hearing things that are not there			✓
Thoughts of killing yourself or trying to kill yourself			✓
Allergic reactions: red, itchy swellings on the skin, swelling of the face, lips, mouth, tongue or throat, difficulty swallowing or breathing, rash or intense itching			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or

- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Always store Xyrem at room temperature (15°- 30°C), in the original bottle in a safe and secure place (locked up if appropriate). Return any unused Xyrem to your pharmacy for proper disposal. Do not pour it down the drain. **Always place your nightly doses of Xyrem safely out of the reach of children**.

Keep out of reach and sight of children and pets.

If you want more information about Xyrem:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html) or by calling 1-866-599-7365.

This leaflet was prepared by Jazz Pharmaceuticals Ireland Limited

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