ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xyrem 500 mg/mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 500 mg of sodium oxybate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

The oral solution is clear to slightly opalescent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of narcolepsy with cataplexy in adult patients, adolescents and children from the age of 7 years.

4.2 Posology and method of administration

Treatment should be initiated by and remain under the guidance of a physician experienced in the treatment of narcolepsy. Physicians should strictly adhere to the contraindications, warnings and precautions.

Posology
Adult
The recommended starting dose is 4.5 g/day sodium oxybate divided into two equal doses of 2.25 g/dose. The dose should be titrated to effect based on efficacy and tolerability (see section 4.4) up to a maximum of 9 g/day divided into two equal doses of 4.5 g/dose by adjusting up or down in dose increments of 1.5 g/day (i.e. 0.75 g/dose). A minimum of one to two weeks is recommended between dose increments. The dose of 9 g/day should not be exceeded due to the possible occurrence of severe symptoms at doses of 18 g/day or above (see section 4.4).

Single doses of 4.5 g should not be given unless the patient has been titrated previously to that dose level.

If sodium oxybate and valproate are used concomitantly (see section 4.5), a decrease in sodium oxybate dose by 20% is recommended. The recommended starting dose for sodium oxybate, when used concomitantly with valproate, is 3.6 g per day administered orally in two equal divided doses of approximately 1.8 g. If concomitant use is warranted, patient response and tolerability should be monitored and dose should be adapted accordingly (see section 4.4).

Discontinuation of Xyrem
The discontinuation effects of sodium oxybate have not been systematically evaluated in controlled clinical trials (see section 4.4).

If the patient stops taking the medicinal product for more than 14 consecutive days, titration should be restarted from the lowest dose.

Special populations

Elderly
Elderly patients should be monitored closely for impaired motor and/or cognitive function when taking sodium oxybate (see section 4.4).

Hepatic impairment
The starting dose should be halved in all patients with hepatic impairment, and response to dose increments monitored closely (see section 4.4 and 5.2).

Renal impairment
All patients with impaired renal function should consider a recommendation to reduce sodium intake (see section 4.4).

Paediatric population

Adolescents and children from 7 years of age with a minimum body weight of 15kg:

Xyrem is administered orally twice nightly. Dosing recommendations are provided in Table 1.

Table 1 Sodium Oxybate Recommended Dose Initiation and Titration for Paediatric Patients

Patient weight	Initial total daily dose (taken in 2 divided doses)*	Titration regimen (to clinical effect)	Recommended maximum total daily dose
15kg - <20kg	≤ 1g/day	≤ 0.5g/day/week	0.2g/kg/day
20kg - <30kg	≤ 2g/day	≤ 1g/day/week	
30kg - <45kg	≤ 3g/day	≤ 1g/day/week	
≥45kg	≤ 4.5g/day	≤ 1.5g/day/week	9g/day

*At bedtime and 2.5 to 4 hours later. For children who sleep more than 8 hours per night, sodium oxybate may be given after bedtime, while the child is in bed, in two equally divided doses 2.5 to 4 hours apart.

The dose should be gradually titrated to effect based on efficacy and tolerability (see section 4.4). A minimum of one to two weeks is recommended between dosage increments. Sodium oxybate dose recommendations (initial dose, titration regimen and maximum dose) for paediatric patients are based on body weight. Therefore, patients should have their body weight checked at regular intervals especially during titration to ensure that the appropriate dose of sodium oxybate is administered.

The recommended maximum total daily dose is 0.2g/kg/day in paediatric patients weighing less than 45kg. For paediatric patients weighing 45kg or more the maximum total daily dose is 9g/day.

If sodium oxybate and valproate are used concomitantly (see section 4.5), a decrease in sodium oxybate dose by 20% is recommended e.g. 4.8g/day instead of 6g/day.

The safety and efficacy of sodium oxybate in children below 7 years of age has not been established and therefore sodium oxybate is not recommended below 7 years of age. Children below 15kg should not receive sodium oxybate.

Method of administration
Xyrem should be taken orally upon getting into bed and again between 2.5 to 4 hours later. It is recommended that both doses of Xyrem should be made up at the same time upon retiring to bed. Xyrem is provided for use with a graduated measuring syringe and two 90 mL dosing cups with child resistant caps. Each measured dose of Xyrem must be dispensed into the dosing cup and diluted with

60 mL of water prior to ingestion. Because food significantly reduces the bioavailability of sodium oxybate, both adult and paediatric patients should eat at least several (2-3) hours before taking the first dose of Xyrem at bedtime. Adult and paediatric patients should always observe the same timing of dosing in relation to meals. Doses should be taken within 24 hours after preparation, or else discarded.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients with major depression.

Patients with succinic semialdehyde dehydrogenase deficiency.

Patients being treated with opioids or barbiturates.

4.4 Special warnings and precautions for use

Xyrem has the potential to induce respiratory depression

Respiratory and CNS depression
Sodium oxybate also has the potential to induce respiratory depression. Patients should be assessed before treatment for sleep apnoea and caution should be exercised when considering treatment. Apnoea and respiratory depression have been observed in a fasting healthy subject after a single intake of 4.5g (twice the recommended starting dose). During post-marketing surveillance, it has been observed that the use of sodium oxybate may predispose the patients to choking sensation during sleep. Patients should be questioned regarding signs of Central Nervous System (CNS) or respiratory depression. Special caution should be observed in patients with an underlying respiratory disorder. Patients should be monitored for signs of respiratory depression during treatment. Because of the higher risk of sleep apnoea, patients with a BMI $\geq$40 kg/m^2 should be monitored closely when taking sodium oxybate.

Approximately 80% of patients who received sodium oxybate during clinical trials maintained CNS stimulant use. Whether this affected respiration during the night is unknown. Before increasing the sodium oxybate dose (see section 4.2), prescribers should be aware that sleep apnoea occurs in up to 50% of patients with narcolepsy.

- *Benzodiazepines*
  Given the possibility of increasing the risk of respiratory depression, the concomitant use of benzodiazepines and sodium oxybate should be avoided.

- *Alcohol and CNS depressants*
  The combined use of alcohol, or any CNS -depressant medicinal product, with sodium oxybate may result in potentiation of the CNS-depressant effects of sodium oxybate as well as increased risk of respiratory depression. Therefore, patients should be warned against the use of alcohol in conjunction with sodium oxybate.

- *Gamma hydroxybutyrate (GHB) dehydrogenase inhibitors*
  Caution is required in patients who are treated concomitantly with valproate or other GHB dehydrogenase inhibitors as pharmacokinetic and pharmacodynamic interactions have been observed when sodium oxybate is co-administered with valproate (see section 4.5). If concomitant use is warranted, dose adjustment is to be considered (see section 4.2). Additionally, patient response and tolerability should be carefully monitored and dose should be adapted accordingly.

- *Topiramate*

There have been clinical observation(s) of coma and increased plasma GHB concentration after co-administration of sodium oxybate with topiramate. Therefore, patients should be warned against the use of topiramate in conjunction with sodium oxybate (section 4.5).

Abuse potential and dependence
Sodium oxybate, which is as the sodium salt of GHB, is a CNS depressant active substance with well-known abuse potential. Prior to treatment physicians should evaluate patients for a history of or susceptibility to drug abuse. Patients should be routinely monitored and in the case of suspected abuse, treatment with sodium oxybate should be discontinued.

There have been case reports of dependence after illicit use of GHB at frequent repeated doses (18 to 250 g/day) in excess of the therapeutic dose range. Whilst there is no clear evidence of emergence of dependence in patients taking sodium oxybate at therapeutic doses, this possibility cannot be excluded.

Patients with porphyria
Sodium oxybate is considered to be unsafe in patients with porphyria because it has been shown to be porphyrogenic in animals or *in vitro* systems.

Neuropsychiatric events
Patients may become confused while being treated with sodium oxybate. If this occurs, they should be evaluated fully, and appropriate intervention considered on an individual basis. Other neuropsychiatric events include anxiety, psychosis, paranoia, hallucinations, and agitation. The emergence of thought disorders including thoughts of committing violent acts (including harming others) and/or behavioural abnormalities when patients are treated with sodium oxybate requires careful and immediate evaluation.

The emergence of depression when patients are treated with sodium oxybate requires careful and immediate evaluation. Patients with a previous history of affective disorders (including depressive illness, anxiety and bipolar disorder), suicide attempt and psychosis should be monitored especially carefully for the emergence of depressive symptoms and/or suicidal ideation while taking sodium oxybate. Major depression is contraindicated for use with sodium oxybate.(see section 4.3).

If a patient experiences urinary or faecal incontinence during sodium oxybate therapy, the prescriber should consider pursuing investigations to rule out underlying aetiologies.

Sleepwalking has been reported in patients treated in clinical trials with sodium oxybate. It is unclear if some or all of these episodes correspond to true somnambulism (a parasomnia occurring during non-REM sleep) or to any other specific medical disorder. The risk of injury or self-harm should be borne in mind in any patient with sleepwalking. Therefore, episodes of sleepwalking should be fully evaluated and appropriate interventions considered.

Paediatric Population:

Monitoring during titration phase
The patient's tolerability, especially with regards to potential signs of central nervous system and respiratory depression, should be carefully monitored with each dose increase during titration. Careful monitoring should include that the parent/caregivers observe the child's breath after sodium oxybate intake to assess if there is any abnormality in breathing during the first two hours, for example rude breathing, sleep apnoea, cyanosis of lips/face. If abnormality in breathing is observed medical support should be sought. If any abnormality is noted after the first dose, the second dose should not be administered. If no abnormality is noted the second dose can be administered. The second dose should not be given earlier than 2.5 hours or later than 4 hours after the first dose. In individual cases, e.g. if it is uncertain that the parent/caregivers can manage careful monitoring as described, sodium oxybate is not recommended unless medical supervision of treatment can be organized.
If in doubt about administration of a dose, do not re-administer the dose to reduce the risk of overdose.

Weight Loss

Weight decrease is common amongst patients treated with sodium oxybate (see section 4.8). For paediatric patients it is important that their weight is checked at regular intervals especially during dose titration to ensure that the appropriate dose of sodium oxybate is being administered (see section 4.2).

Neuropsychiatric events
For children and adolescents extra care should be taken to assess any potential suicidal or depressive conditions before starting treatment with sodium oxybate (see section 4.8) and to monitor any treatment-emergent events.

Alcohol and CNS depressants
Given the risk of alcohol intake among adolescents, it is noted that alcohol may further increase the CNS and respiratory depressant effects of sodium oxybate in children – adolescents taking sodium oxybate (see section 4.5).

Sodium intake
This medicinal product contains 182.24 mg sodium per 1 g of sodium oxybate dose, equivalent to 9.11% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
The maximum daily dose of this product is equivalent to 82% of the WHO recommended maximum daily intake for sodium.
Xyrem is considered high in sodium. This should be particularly taken into account for those on a low salt diet.
A recommendation to reduce sodium intake should be carefully considered in the management of patients with heart failure, hypertension or compromised renal function (see section 4.2 and 4.9)

Elderly
There is very limited experience with sodium oxybate in the elderly. Therefore, elderly patients should be monitored closely for impaired motor and/or cognitive function when taking sodium oxybate.

Epileptic patients
Seizures have been observed in patients treated with sodium oxybate. In patients with epilepsy, the safety and efficacy of sodium oxybate has not been established, therefore use is not recommended.

Rebound effects and withdrawal syndrome
The discontinuation effects of sodium oxybate have not been systematically evaluated in controlled clinical trials. In some patients, cataplexy may return at a higher frequency on cessation of sodium oxybate therapy, however this may be due to the normal variability of the disease. Although the clinical trial experience with sodium oxybate in narcolepsy/cataplexy patients at therapeutic doses does not show clear evidence of a withdrawal syndrome, in rare cases, events such as insomnia, headache, anxiety, dizziness, sleep disorder, somnolence, hallucination, and psychotic disorders were observed after GHB discontinuation.

Educational Materials
In order to assist prescribers, and patients/caregivers about the important information for Xyrem educational materials will be provided to them. In particular the materials will reinforce that for paediatric patients, an initial assessment of the patient should be performed with regard to growth and learning ability and that in addition to any side effects, any behaviour changes (social and learning), should be reported to the child's healthcare provider.

4.5 Interaction with other medicinal products and other forms of interaction

The combined use of alcohol with sodium oxybate may result in potentiation of the central nervous system-depressant effects of sodium oxybate. Patients should be warned against the use of any alcoholic beverages in conjunction with sodium oxybate.

Sodium oxybate should not be used in combination with sedative hypnotics or other CNS depressants.

Sedative hypnotics
Drug interaction studies in healthy adults with sodium oxybate (single dose of 2.25 g) and lorazepam (single dose of 2 mg) and zolpidem tartrate (single dose of 5 mg) demonstrated no pharmacokinetic interactions. Increased sleepiness was observed after concomitant administration of sodium oxybate (2.25 g) and lorazepam (2 mg). The pharmacodynamic interaction with zolpidem has not been assessed. When higher doses up to 9 g/d of sodium oxybate are combined with higher doses of hypnotics (within the recommended dose range) pharmacodynamic interactions associated with symptoms of CNS depression and/or respiratory depression cannot be excluded (see section 4.3).

Tramadol
A drug interaction study in healthy adults with sodium oxybate (single dose of 2.25 g) and tramadol (single dose of 100 mg) demonstrated no pharmacokinetic/pharmacodynamic interaction. When higher doses up to 9 g/day of sodium oxybate are combined with higher doses of opioids (within the recommended dose range) pharmacodynamic interactions associated with symptoms of CNS depression and/or respiratory depression cannot be excluded (see sections 4.3).

Antidepressants
Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate (single dose of 2.25 g) and the antidepressants protriptyline hydrochloride (single dose of 10 mg) and duloxetine (60 mg at steady state). No additional effect on sleepiness was observed when comparing single doses of sodium oxybate alone (2.25 g) and sodium oxybate (2.25 g) in combination with duloxetine (60 mg at steady state). Antidepressants have been used in the treatment of cataplexy. A possible additive effect of antidepressants and sodium oxybate cannot be excluded. The rate of adverse reactions has increased when sodium oxybate is co-administered with tricyclic antidepressants.

Modafinil
A drug interaction study in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate (single dose of 4.5 g) and modafinil (single dose of 200 mg). Sodium oxybate has been administered concomitantly with CNS stimulant agents in approximately 80% of patients in clinical studies in narcolepsy. Whether this affected respiration during the night is unknown.

Omeprazole
The co-administration of omeprazole has no clinically significant effect on the pharmacokinetics of sodium oxybate. The dose of sodium oxybate therefore does not require adjustment when given concomitantly with proton pump inhibitors.

Ibuprofen
Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and ibuprofen.

Diclofenac
Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and diclofenac. Co-administration of sodium oxybate and diclofenac in healthy volunteers reduced the attention deficit caused by the administration of sodium oxybate alone as measured by psychometric tests.

GHB dehydrogenase inhibitors
Since sodium oxybate is metabolised by GHB dehydrogenase there is a potential risk of an interaction with medicinal products that stimulate or inhibit this enzyme (e.g. valproate, phenytoin or ethosuximide) (see section 4.4).

The co-administration of sodium oxybate (6 g per day) with valproate (1250 mg per day) resulted in an increase in systemic exposure to sodium oxybate by approximately 25% and no significant change in $C_{max.}$ No effect on the pharmacokinetics of valproate was observed. The resulting

pharmacodynamic effects, including increased impairment in cognitive function and sleepiness, were greater with co-administration than those observed with either drug alone. If concomitant use is warranted, patient response and tolerability should be monitored and dose adjustments made if required (see section 4.2).

Topiramate
Possible pharmacodynamic and pharmacokinetic interactions when sodium oxybate is used concomitantly with topiramate cannot be excluded as clinical observation(s) of coma, and increased plasma GHB concentration were reported in a patient(s) under concomitant use of sodium oxybate and topiramate (section 4.4).

Studies *in vitro* with pooled human liver microsomes indicate that sodium oxybate does not significantly inhibit the activities of the human isoenzymes (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies have shown no evidence of teratogenicity but embryo lethality was seen in both rat and rabbit studies (see section 5.3).

Data from a limited number of pregnant women exposed in the first trimester indicate a possible increased risk of spontaneous abortions. To date no other relevant epidemiological data are available. Limited data from pregnant patients during second and third trimester indicate no malformative or foeto/neonatal toxicity of sodium oxybate.

Sodium oxybate is not recommended during pregnancy.

Breast-feeding
Sodium oxybate and/or its metabolites are excreted into breast milk. Changes in sleep patterns have been observed in breastfed infants from exposed mothers, which may be consistent with the effects of sodium oxybate on the nervous system. Sodium Oxybate should not be used during breastfeeding.

Fertility
There is no clinical data available on the effect of sodium oxybate on fertility. Studies in male and female rats at doses up to 1,000 mg/kg/day GHB have shown no evidence of an adverse effect on fertility.

4.7 Effects on ability to drive and use machines

Sodium oxybate has major influence on the ability to drive and use machines.

For at least 6 hours after taking sodium oxybate, patients must not undertake activities requiring complete mental alertness or motor co-ordination, such as operating machinery or driving.
When patients first start taking sodium oxybate, until they know whether this medicinal product will still have some carryover effect on them the next day, they should use extreme care while driving a car, operating heavy machines, or performing any other task that could be dangerous or require full mental alertness.

For paediatric patients, physicians and parents or caregivers are advised that if the daily dose to body weight ratio exceeds 0.1g/kg/day, the waiting time may be longer than 6 hours depending on individual sensitivity.

4.8 Undesirable effects

Summary of the safety profile

Clinical Studies

The safety profile was qualitatively the same in adult and paediatric studies.

In adults the most commonly reported adverse reactions were dizziness, nausea, and headache, all occurring in 10% to 20% of patients. The most serious adverse reactions are suicidal attempt, psychosis, respiratory depression and convulsion.

In adults the efficacy and safety of sodium oxybate for the treatment of narcolepsy symptoms was established in four multicentre, randomised, double-blind, placebo-controlled, parallel-group trials in patients with narcolepsy with cataplexy except for one trial where cataplexy was not required for enrolment. Two Phase 3 and one Phase 2 double-blind, parallel-group, placebo-controlled studies were performed to assess the indication of sodium oxybate for fibromyalgia in adults. Additionally, randomised, double-blind, placebo-controlled, crossover drug-drug interaction studies with ibuprofen, diclofenac and valproate were performed in healthy adult subjects and are summarised in section 4.5.

Post-marketing experience
In addition to the adverse reactions reported during clinical studies, adverse reactions have been reported in post-marketing experience. It is not always possible to reliably estimate the frequency of their incidence in the population to be treated.

Tabulated summary of adverse reactions
Undesirable effects are listed according to MedDRA System Organ Class.

Frequency estimate: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations
Common: nasopharyngitis, sinusitis

Immune system disorders
Uncommon: hypersensitivity

Metabolism and nutrition disorders
Common: anorexia, decreased appetite
Not known: Dehydration, increased appetite

Psychiatric disorders
Common: depression, cataplexy, anxiety, abnormal dreams, confusional state, disorientation, nightmares, sleepwalking, sleep disorder, insomnia, middle insomnia, nervousness
Uncommon: suicide attempt, psychosis, paranoia, hallucination, abnormal thinking, agitation, initial insomnia
Not known: suicidal ideation, homicidal ideation, aggression, euphoric mood, sleep-related eating disorder, panic attack, mania / bipolar disorder, delusion, bruxism, irritability and increased libido

Nervous system disorders
Very common: dizziness, headache
Common: sleep paralysis, somnolence, tremor, balance disorder, disturbance in attention, hypoaesthesia, paraesthesia, sedation, dysgeusia
Uncommon: myoclonus, amnesia, restless legs syndrome
Not known: convulsion, loss of consciousness, dyskinesia

Eye disorders
Common: blurred vision

Ear and labyrinth disorders
Common: vertigo
Not known tinnitus

Cardiac disorders
Common: palpitations

Vascular disorders
Common: hypertension

Respiratory, thoracic and mediastinal disorders
Common: dyspnoea, snoring, nasal congestion
Not known: respiratory depression, sleep apnoea, choking sensation

Gastrointestinal disorders
Very common: nausea (the frequency of nausea is higher in women than men)
Common: vomiting, diarrhoea, abdominal pain upper,
Uncommon: faecal incontinence
Not known: dry mouth

Skin and subcutaneous tissue disorders
Common: hyperhidrosis, rash
Not known: urticaria, angioedema, seborrhea

Musculoskeletal and connective tissue disorders
Common: arthralgia, muscle, spasms, back pain

Renal and urinary disorders
Common: enuresis nocturna, urinary incontinence
Not known: pollakiuria / micturition urgency, nocturia

General disorders and administration site conditions
Common: asthenia, fatigue, feeling drunk, oedema peripheral

Investigations
Common: blood pressure increased, weight decreased

Injury, poisoning and procedural complications
Common: fall

Description of selected adverse reactions
In some patients, cataplexy may return at a higher frequency on cessation of sodium oxybate therapy, however this may be due to the normal variability of the disease. Although the clinical trial experience with sodium oxybate in narcolepsy/cataplexy patients at therapeutic doses does not show clear evidence of a withdrawal syndrome, in rare cases, adverse reactions such as insomnia, headache, anxiety, dizziness, sleep disorder, somnolence, hallucination, and psychotic disorders were observed after GHB discontinuation.

Special Populations

Paediatric population
In the paediatric population the efficacy and safety of sodium oxybate for the treatment of narcolepsy with cataplexy symptoms was established in a phase 2/3 double-blind, placebo-controlled, randomized-withdrawal multicenter study.

In a study in children and adolescents the most frequently reported related TEAEs were enuresis (18.3%), nausea (12.5%), vomiting (8.7%), and weight decreased (8.7%), decreased appetite (6.7%),

headache (5.8%), dizziness (5.8%). Adverse drug reactions of suicidal ideation (1%) and of acute psychosis (1%) were also reported. (see section 4.4 and section 5).

In some children between 7 and < 18 years, postmarketing surveillance has shown that sodium oxybate was discontinued due to abnormal behaviour, aggression and mood alteration.

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Information about signs and symptoms associated with overdose with sodium oxybate is limited. Most data derives from the illicit use of GHB. Sodium oxybate is the sodium salt of GHB. Events associated with withdrawal syndrome have been observed outside the therapeutic range.

Symptoms
Patients have exhibited varying degrees of depressed consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even with impaired consciousness), diaphoresis, headache, and impaired psychomotor skills may be observed. Blurred vision has been reported. An increasing depth of coma has been observed at higher doses as well as acidosis. Myoclonus and tonic-clonic seizures have been reported. There are reports of compromise in the rate and depth of respiration and of life-threatening respiratory depression, necessitating intubation and ventilation. Cheyne-Stokes respiration and apnoea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact. Bradycardia has been responsive to atropine intravenous administration**.** Events of hypernatremia with metabolic alkalosis have been reported in the context of concomitant use of NaCl infusion.

Management
Gastric lavage may be considered if co-ingestants are suspected. Because emesis may occur in the presence of impaired consciousness, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although 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.

No reversal of the central depressant effects of sodium oxybate can be expected from flumazenil administration. There is insufficient evidence to recommend the use of naloxone in the treatment of overdose with GHB. The use of haemodialysis and other forms of extracorporeal medicinal product removal have not been studied in sodium oxybate overdose, but has been reported in cases of acidosis due to GHB overdose. However, due to the rapid metabolism of sodium oxybate, these measures may not be warranted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC code: N07XX04.

Mechanism of action
Sodium oxybate is a central nervous system depressant which reduces excessive daytime sleepiness and cataplexy in patients with narcolepsy and modifies sleep architecture reducing fragmented nighttime sleep. The precise mechanism by which sodium oxybate produces an effect is unknown, however sodium oxybate is thought to act by promoting slow (delta) wave sleep and consolidating

night-time sleep. Sodium oxybate administered before nocturnal sleep increases Stages 3 and 4 sleep and increases sleep latency, whilst reducing the frequency of sleep onset REM periods (SOREMPs). Other mechanisms, which have yet to be elucidated, may also be involved. In the clinical trial database, greater than 80 % of patients maintained concomitant stimulant use.

Adults

The effectiveness of sodium oxybate for the treatment of narcolepsy symptoms was established in four multicentre, randomised, double-blind, placebo-controlled, parallel-group trials (Trial 1, 2, 3 and 4) in patients with narcolepsy with cataplexy except for trial 2 where cataplexy was not required for enrolment Concomitant stimulant use was permitted in all trials (except for the active-treatment phase of Trial 2); antidepressants were withdrawn prior to active treatment in all trials with the exception of Trial 2. In each trial, the daily dose was 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.

Table 2 Summary of clinical trials performed using sodium oxybate for the treatment of narcolepsy

Trial	Primary Efficacy	N	Secondary Efficacy	Duration	Active treatment and Dose (g/d)
Trial 1	EDS (ESS); CGIc	246	MWT/Sleep Architecture/ Cataplexy/Naps/FOSQ	8 weeks	Sodium oxybate4.5 - 9
Trial 2	EDS (MWT)	231	Sleep Architecture/ ESS/CGIc/Naps	8 weeks	Sodium oxybate 6 – 9 Modafinil 200-600 mg
Trial 3	Cataplexy	136	EDS (ESS)/CGIc/Naps	4 weeks	Sodium oxybate 3 - 9
Trial 4	Cataplexy	55	None	4 weeks	Sodium oxybate 3 - 9

EDS – Excessive daytime sleepiness; ESS – Epworth Sleepiness Scale; MWT – Maintenance of Wakefulness Test; Naps – Number of inadvertent daytime naps; CGIc – Clinical Global Impression of Change; FOSQ – Functional Outcomes of Sleep Questionnaire

Trial 1 enrolled 246 patients with narcolepsy and incorporated a 1 week up-titration period. The primary measures of efficacy were changes in excessive daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS), and the change in the overall severity of the patient's narcolepsy symptoms as assessed by the investigator using the Clinical Global Impressions of Change (CGI-c) measure.

Table 3 Summary of ESS in Trial 1

Epworth Sleepiness Scale (ESS; range 0-24)				
Dose Group [g/d (n)]	Baseline	Endpoint	Median Change from Baseline	Change from Baseline Compared to Placebo (p-value)
Placebo (60)	17.3	16.7	-0.5	-
4.5 (68)	17.5	15.7	-1.0	0.119
6 (63)	17.9	15.3	-2.0	0.001
9 (55)	17.9	13.1	-2.0	< 0.001

Table 4 Summary of CGI-c in Trial 1

Clinical Global Impressions of Change (CGI-c)		
Dose Group [g/d (n)]	Responders* N (%)	Change from Baseline Compared to Placebo (p-value)
Placebo (60)	13 (21.7)	-
4.5 (68)	32 (47.1)	0.002
6 (63)	30 (47.6)	< 0.001
9 (55)	30 (54.4)	< 0.001

* The CGI-c data were analysed by defining responders as those patients who were very much improved or much improved.

Trial 2 compared the effects of orally administered sodium oxybate, modafinil and sodium oxybate + modafinil, with placebo in the treatment of daytime sleepiness in narcolepsy. During the 8 week double-blind period, patients took modafinil at their established dose or placebo equivalent. The sodium oxybate or placebo equivalent dose was 6 g/day for the first 4 weeks and was increased to 9 g/day for the remaining 4 weeks. The primary measure of efficacy was excessive daytime sleepiness as measured by objective response in MWT.

Table 5 Summary of MWT in Trial 2

TRIAL 2				
Dose Group	Baseline	Endpoint	Mean Change from Baseline	Endpoint Compared to Placebo
Placebo (56)	9.9	6.9	-2.7	-
Sodium Oxybate (55)	11.5	11.3	0.16	<0.001
Modafinil (63)	10.5	9.8	-0.6	0.004
Sodium Oxybate + Modafinil (57)	10.4	12.7	2.3	<0.001

Trial 3 enrolled 136 narcoleptic patients with moderate to severe cataplexy (median of 21 cataplexy attacks per week) at baseline. The primary efficacy measure in this trial was the frequency of cataplexy attacks.

Table 6 Summary of outcomes in Trial 3

Dosage	**Number of Subjects**	**Cataplexy Attacks**		
Trial 3		Baseline	Median Change from Baseline	Change from Baseline Compared to Placebo (p-value)
		Median attacks/week		
Placebo	33	20.5	-4	-
3.0 g/day	33	20.0	-7	0.5235
6.0 g/day	31	23.0	-10	0.0529
9.0 g/day	33	23.5	-16	0.0008

Trial 4 enrolled 55 narcoleptic patients who had been taking open-label sodium oxybate for 7 to 44 months. Patients were randomised to continued treatment with sodium oxybate at their stable dose

or to placebo. Trial 4 was designed specifically to evaluate the continued efficacy of sodium oxybate after long-term use. The primary efficacy measure in this trial was the frequency of cataplexy attacks.

Table 7 Summary of outcome in Trial 4

Treatment Group	**Number of Subjects**	**Cataplexy Attacks**		
Trial 4		Baseline	Median Change from Baseline	Change from Baseline Compared to Placebo (p-value)
		Median attacks/two weeks		
Placebo	29	4.0	21.0	-
Sodium oxybate	26	1.9	0	p <0.001

In Trial 4, the response was numerically similar for patients treated with doses of 6 to 9 g/day, but there was no effect seen in patients treated with doses less than 6 g/day.

Paediatric population

The effectiveness of sodium oxybate in paediatric patients with narcolepsy with cataplexy, was established in a double-blind, placebo-controlled, randomized-withdrawal, multicentre trial.

This study demonstrated the clinical efficacy of sodium oxybate in the treatment of cataplexy and Excess Daytime Sleepiness (EDS) in narcolepsy in pediatric subjects.
63 patients were randomized in the efficacy population where the primary efficacy endpoint in this trial was the change in number of weekly cataplexy attacks between the last two weeks of the stable dose period and the double-blind period.

During the double-blind period, the median (Q1, Q3) change from baseline (i.e. the last 2 weeks of the stable dose period) in the weekly number of cataplexy attacks was 12.71 (3.44, 19.77) for patients randomized to placebo and 0.27 (-1.00, 2.50) for patients randomized to sodium oxybate.

Table 8 Summary of outcome in study 13-005 in children / adolescents

Treatment Group	**Number of Patients**	**Weekly Number of Cataplexy Attacks (median)**		
		Baseline (i.e. Last 2 weeks of stable dose period)	**Double-blind period**	**Change from Baseline**
Placebo	32	4.67	21.25	12.71
Sodium oxybate	31	3.50	3.77	0.27
p-value				< 0.0001

When subgroup analyses by age group (7-11 years and 12-17 years) were conducted for the primary endpoint, similar results were observed. During the Double-blind Treatment Period, among subjects aged 7 to 11 years, the median (Q1, Q3) change from baseline in the weekly number of cataplexy attacks was 18.32 (7.58, 35.75) for subjects randomized to Placebo and 0.13 (-1.15, 2.05) for subjects randomized to sodium oxybate ($p < 0.0001$). During the Double-blind Treatment Period, among subjects aged 12 to 17 years, the median (Q1, Q3) change from baseline in the weekly number of cataplexy attacks was 9.39 (1.08, 16.12) for subjects randomized to Placebo and 0.58 (-0.88, 2.58) for subjects randomized to sodium oxybate ($p = 0.0044$)

During the Double-blind Treatment Period, the median (Q1, Q3) change of the secondary endpoint (change in ESS scores) from baseline (which occurred at Visit 3 – the end of the Stable Dose Period) in Epworth Sleepiness Scale for Children and Adolescent (ESS-CHAD) score was 3.0 (1.0, 5.0) for subjects randomized to Placebo and 0.0 (-1.0, 2.0) for subjects randomized to sodium oxybate. The comparison of the rank change from baseline between treatments was statistically significant ($p = 0.0004$) when analyzed by ANCOVA modeling containing treatment as a factor and rank baseline value as a covariate. Subjects randomized to Placebo had, on average, higher ESS (CHAD) scores at baseline compared to those on sodium oxybate.

Table 9 Summary of ESS (CHAD) Score during the Double-blind Treatment Period (Efficacy Population)

Treatment Group	**Number of Patients**	**Change in ESS (CHAD) Score (median)**		
		Baseline (Visit 3-End of Stable Dose Period)	**End of Double-blind Treatment Period** (Visit 4**)**	**Change from Baseline**
Placebo	32	11.0	12.0	3.0
Sodium oxybate	31	8.0	9.0	0.0
p-value				0.0004

Abbreviations: ESS (CHAD) = Epworth Sleepiness Scale for Children and Adolescents

5.2 Pharmacokinetic properties

Sodium oxybate is rapidly and almost completely 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 is nonlinear with the area under the plasma concentration curve (AUC) versus time curve increasing 3.8-fold as dose is doubled from 4.5 g to 9 g. The pharmacokinetics is 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 2 hours in eight pharmacokinetic studies. Following oral administration, the plasma levels of sodium oxybate increase 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 190-384 mL/kg. At sodium oxybate concentrations ranging from 3 to 300 µg/mL, less than 1% is bound to plasma proteins.

Biotransformation

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 β-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 metabolised 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 Acetyl CoA, which also enters the citric acid cycle to result in the formation of carbon dioxide and water. No active metabolites have been identified.

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). These levels are considerably higher than levels achieved with therapeutic doses.

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 medicinal product appears in human urine within 6 to 8 hours after dosing. Faecal excretion is negligible.

Special populations

Elderly

In a limited number of patients greater than the age of 65 years the pharmacokinetics of sodium oxybate was not different compared to patients younger than 65 years of age.

Paediatric population

The major pharmacokinetic characteristics of sodium oxybate in paediatric subjects are the same as those reported in pharmacokinetic studies of sodium oxybate in adults

Paediatric and adult subjects receiving the same mg/kg dose have similar plasma concentration-time profiles. (see section 4.2)

Renal impairment

Because the kidney does not have a significant role in the excretion of sodium oxybate, no pharmacokinetic study in patients with renal dysfunction has been conducted; no effect of renal function on sodium oxybate pharmacokinetics would be expected.

Hepatic impairment
Sodium oxybate undergoes significant presystemic (hepatic first-pass) metabolism. After a single oral dose of 25 mg/kg, AUC values were double in cirrhotic patients, with apparent oral clearance reduced from 9.1 in healthy adults to 4.5 and 4.1 mL/min/kg in Class A (without ascites) and Class C (with ascites) patients, respectively. Elimination half-life was significantly longer in Class C and Class A patients than in control subjects (mean t1/2 of 59 and 32 versus 22 minutes). The starting dose should be halved in all patients with hepatic impairment, and response to dose increments monitored closely (see section 4.2).

Race
The effect of race on metabolism of sodium oxybate has not been evaluated.

5.3 Preclinical safety data

Repeat administration of sodium oxybate to rats (90 days and 26 weeks) and dogs (52 weeks) did not result in any significant findings in clinical chemistry and micro- and macro pathology. Treatment-related clinical signs were mainly related to sedation, reduced food consumption and secondary changes in body weight, body weight gain and organ weights. The rat and dog exposures at the NOEL were lower (~50%) than that in humans. Sodium oxybate was non-mutagenic and non-clastogenic in *in vitro* and *in vivo* assays.

Gamma Butyrolactone (GBL), a pro-drug of GHB tested at exposures similar to the expected in man (1.21-1.64 times) has been classified by NTP as non-carcinogenic in rats and equivocal carcinogen in mice, due to slight increase of pheochromocytomas which was difficult to interpret due to high mortality in the high dose group. In a rat carcinogenicity study with oxybate no compound-related tumours were identified.

GHB had no effect on mating, general fertility or sperm parameters and did not produce embryo-foetal toxicity in rats exposed to up 1000 mg/kg/day GHB (1.64 times the human exposure calculated in nonpregnant animals). Perinatal mortality was increased and mean pup weight was decreased during the lactation period in high-dose F_1 animals. The association of these developmental effects with maternal toxicity could not be established. In rabbits, slight foetotoxicity was observed.

In a 10-week repeat dose toxicity study conducted in juvenile rats treated from postnatal day 21 to 90, sodium oxybate produced adverse effects including mortalities during the first week of treatment, when animals were 21 to 27 days old, corresponding to an approximate age of 3-4 years in children. Acute toxicity appeared at exposures below those expected in paediatric patients and mortality was preceded by sodium oxybate-related clinical signs (bradypnea, deep breathing, decreased activity, uncoordinated gait, impaired righting reflex), in line with its expected pharmacology. The reason for this relatively stronger toxicity during the first week of treatment is not fully clear. It could be related to the fact that young animals appear to exhibit higher systemic exposure than older juvenile rats. It could also be due to higher sensitivity of pups to sodium oxybate compared to older juvenile and adult rats and/or to a tolerance development phenomenon. Reduced body weight and food consumption similarly as in adults were also observed, with additional respiratory signs (deep and slow breathing). Sodium oxybate did not produce adverse effects on growth and development up to exposure levels 2- to 4-fold higher than the exposure expected at the maximum recommended dose in paediatric subjects (200mg/kg/day in paediatric patients with body weight less than 45kg or 9g/day for paediatric patients with body weight $\geq$ 45kg).

Drug discrimination studies show that GHB produces a unique discriminative stimulus that in some respects is similar to that of alcohol, morphine and certain GABA-mimetic medicinal products. Self-administration studies in rats, mice and monkeys have produced conflicting results, whereas tolerance to GHB as well as cross-tolerance to alcohol and baclofen has been clearly demonstrated in rodents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified water
Malic acid for pH adjustment
Sodium hydroxide for pH adjustment

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

5 years

After first opening**:** 90 days

After dilution in the dosing cups, the preparation should be used within 24 hours.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after first opening of the medicinal product, see section 6.3
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use

180 mL solution in an amber oval 240 mL PET bottle which is delivered with a plastic/foil seal and closed with a child resistant closure composed of HDPE/polypropylene with a pulpboard inner liner.

Each carton contains one bottle, a press-in bottle adaptor, a graduated measuring device (polypropylene syringe), two polypropylene dosing cups and two HDPE child resistant screw closures.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Brussels
Belgium

8. MARKETING AUTHORISATION NUMBER

EU/1/05/312/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date for first authorisation: 13 October 2005
Date of latest renewal: 08 September 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

UCB Pharma S.A.,
Chemin du Foriest,
B-1420 Braine l'Alleud,
Belgium

B CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to special and restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall develop an educational programme for Xyrem to ensure that physicians who intend to prescribe Xyrem are aware about the posology of Xyrem and the important risks. The five components of this comprehensive program are:

- Healthcare Professional Checklist (i.e. forms for treatment initiation and follow-up visits) : to remind physicians to check the following:
    a. contraindications, warnings, and precautions in the SmPC and specifically highlighting that Xyrem can cause CNS and respiratory depression, that alcohol may result in the potentiation of CNS depression and that Xyrem has an abuse potential.
    b. For pediatric patients: height, weight, learning, social and psychiatric behaviour

- Frequently Asked Questions (FAQ) for patients (to be given to the patient): to provide patients with responses to some questions they might have about taking Xyrem.
- Patient instructions for administration of sodium oxybate (to be given to the patient): to provide patients with information related to the use of Xyrem.
- Xyrem guide for pediatric patients and their caregivers to provide information about the safe use and handling of sodium oxybate.
- Patient Alert Card (to be given to the patient): to remind patients, caregivers, and physicians of the important safety information related to the use of Xyrem.

The MAH has established a controlled distribution program that enhances existing controls for Xyrem to allow reaching the intended population of narcolepsy patients while minimizing the risk of Xyrem being diverted by those seeking to misuse it.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE OUTER PACKAGING

Carton and bottle

1. NAME OF THE MEDICINAL PRODUCT

Xyrem 500 mg/mL oral solution
Sodium oxybate

2. STATEMENT OF ACTIVE SUBSTANCE

Each mL of solution contains 500 mg sodium oxybate

3. LIST OF EXCIPIENTS

High in sodium – see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

One bottle of 180 mL oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

The medicinal product should be used within 90 days after the first opening.
After dilution in the dosing cups the preparation should be used within 24 hours.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/05/312/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xyrem 500 mg/mL (applies to carton only)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Xyrem 500 mg/mL oral solution
Sodium oxybate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Xyrem is and what it is used for

Xyrem contains the active substance sodium oxybate. Xyrem works by consolidating night-time sleep, though its exact mechanism of action is unknown.

Xyrem is used to treat narcolepsy with cataplexy in adults, adolescents and children from 7 years of age.

Narcolepsy is a sleep disorder that may include attacks of sleep during normal waking hours, as well as cataplexy, sleep paralysis, hallucinations and poor sleep. Cataplexy is the onset of sudden muscle weakness or paralysis without losing consciousness, in response to a sudden emotional reaction such as anger, fear, joy, laughter or surprise.

2. What you need to know before you take Xyrem

Do not take Xyrem
- if you are allergic to sodium oxybate or any of the other ingredients of this medicine (listed in section 6);
- if you have succinic semialdehyde dehydrogenase deficiency (a rare metabolic disorder);
- if you suffer from major depression;
- if you are being treated with opioid or barbiturate medicines.

Warnings and precautions
Talk to your doctor or pharmacist before taking Xyrem:
- if you have breathing or lung problems (and especially if you are obese), because Xyrem has the potential to cause difficulty in breathing;
- if you have or have previously had depressive illness, suicidal thoughts, anxiety, psychosis (a mental disorder that may involve hallucinations, incoherent speech, or disorganized and agitated behaviour) or bipolar disorder
- if you have heart failure, hypertension (high blood pressure), liver or kidney problems as your dose may need to be adjusted;
- if you have previously abused drugs;
- if you suffer from epilepsy as the use of Xyrem is not recommended in this condition;

- if you have porphyria (an uncommon metabolic disorder).

If any of these apply to you, tell your doctor before you take Xyrem.

While you are taking Xyrem, if you experience bed wetting and incontinence (both urine and faeces), confusion, hallucinations, episodes of sleepwalking or abnormal thinking you should tell your doctor straight away. Whilst these effects are uncommon, if they do occur they are usually mild-to-moderate in nature.

If you are elderly, your doctor will monitor your condition carefully to check whether Xyrem is having the desired effects.

Xyrem has a well-known abuse potential. Cases of dependency have occurred after the illicit use of sodium oxybate.

Your doctor will ask if you have ever abused any drugs before you start taking Xyrem and whilst you are using the medicine.

Children and adolescents
Xyrem can be taken by adolescents and children from 7 years of age when they are over 15 kg in weight.

Xyrem cannot be taken by children below 7 years of age or below 15 kg in weight.

If you are a child or adolescent, your doctor will monitor your body weight regularly.

Whilst the doctor is adjusting the dose which may take a number of weeks, parent/caregivers should carefully monitor the child's breath during the first 2 hours after sodium oxybate intake to assess if there is any abnormality in breathing, for example stoppage of breathing for short periods while sleeping, noisy breathing and bluish colour of the lips and face. If abnormality in breathing is observed medical support should be sought and the doctor should be informed as soon as possible. If any abnormality is noted after the first dose, the second dose should not be administered. If no abnormality is noted the second dose can be administered. The second dose should not be given earlier than 2.5 hours or later than 4 hours after the first dose.

If you have had or are having upsetting feelings particularly if you are feeling very sad or have lost interest in life it is important that you tell the doctor or caregiver.

Other medicines and Xyrem
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular Xyrem should not be taken together with sleep inducing medicines and medicines that reduce central nervous system activity (the central nervous system is the part of the body related to the brain and spinal cord).

Also tell your doctor or pharmacist if you are taking any of the following types of medicines:
- medicines that increase central nervous system activity
- antidepressants
- medicines that may be processed in a similar way by the body (e.g., valproate, phenytoin or ethosuximide which are used for the treatment of fits)
- topiramate (used for treatment of epilepsy)

If you are taking Valproate, your daily dose of Xyrem will need to be adjusted (see section 3) as it may lead to interactions with Valproate

Xyrem with alcohol
You must not drink alcohol while taking Xyrem, as its effects can be increased.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
There have been very few women who have taken Xyrem sometime during their pregnancy and a few of them had spontaneous abortions. The risk of taking Xyrem during pregnancy is unknown, and, therefore, the use of Xyrem in pregnant women or women trying to become pregnant is not recommended.

Patients taking Xyrem should not breast feed since it is known that Xyrem passes into breast milk. Changes in sleep patterns have been observed in breastfed infants from exposed mothers.

Driving and using machines
Xyrem will affect you if you drive or operate tools or machines. Do not drive a car, operate heavy machinery, or perform any activity that is dangerous or that requires mental alertness for at least 6 hours after taking Xyrem. When you first start taking Xyrem, until you know whether it makes you sleepy the next day, use extreme care while driving a car, operating heavy machinery or doing anything else that could be dangerous or needs you to be fully mentally alert.

For paediatric patients, physicians, parents or caregivers are advised that the waiting time for performing activities that require mental alertness, motor co-ordination or any activities that may have a physical risk may have to be longer than 6 hours, depending on individual sensitivity.

Xyrem contains sodium
This medicine contains 182.24 mg sodium (main component of cooking/table salt) in each gram. This is equivalent to 9.11% of the recommended maximum daily dietary intake of sodium for an adult. Talk to your doctor or pharmacist if you need 2 g of sodium oxybate (Xyrem) or more daily for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.

3. How to take Xyrem

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

It is important that you only use the syringe provided in the box when preparing doses of Xyrem. The Xyrem syringe has two different measurement scales, one scale may be more helpful for you than the other depending on which dose your doctor has prescribed. By looking at each scale you will see which one provides the exact mark for your dose.

Adults – taking Xyrem on its own
- For adults the recommended starting dose is 4.5 g each day, given as two seperate doses of 2.25 g.
- Your doctor may gradually increase your dose up to a maximum of 9 g each day given as two separate doses of 4.5 g.
- Take Xyrem orally two times each night:
  - Take the first dose upon getting into bed and the second dose 2½ to 4 hours later. You may need to set an alarm clock to make sure you wake up to take the second dose.
  - Food decreases the amount of Xyrem that is absorbed by your body. Therefore, it is best to take Xyrem at set times 2 to 3 hours after a meal.
  - Prepare both doses before bedtime.
  - Take doses within 24 hours after preparation.

Adolescents and children aged 7 years and over who weigh 15 kg or more - taking Xyrem on its own

For those aged 7 years and over who weigh 15 kg or more, a doctor will work out the right dose based on your body weight.

Your doctor will work out the right dose for you. Do not exceed the dose prescribed for you.

Adults - taking Xyrem with Valproate
If you are taking valproate together with Xyrem, the dose of Xyrem will be adapted by your doctor.

- For adults the recommended starting dose for Xyrem, when used together with Valproate, is 3.6 g each day, given as two separate doses of 1.8 g.
- Take the first dose when getting into bed and the second dose 2½ to 4 hours later.

Adolescents and children aged 7 years and older who weigh 15 kg or more - taking Xyrem with Valproate
If you are taking Valproate together with Xyrem, the dose of Xyrem will be adapted by your doctor.

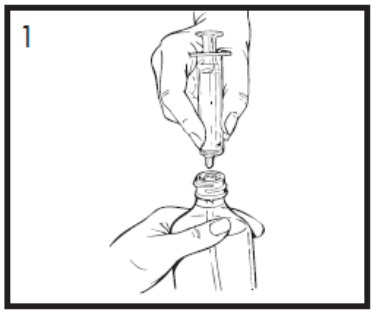
Kidney or liver problems
- If you have kidney problems, you should consider a dietary recommendation to reduce sodium (salt) intake. If you have liver problems, the starting dose should be halved. Your doctor may gradually increase your dose.

Instructions on how to dilute Xyrem

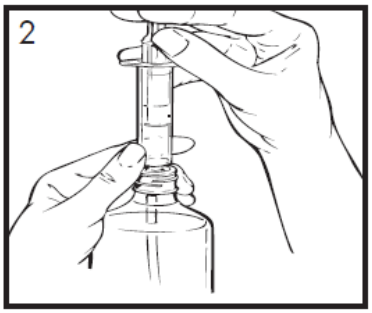
The following instructions explain how to prepare Xyrem. Please read the instructions carefully and follow them step by step. Do not allow children to prepare Xyrem.

To help you, the Xyrem carton contains 1 bottle of medicine, a measuring syringe (with two different measurement scales) and two dosing cups with child-resistant caps.

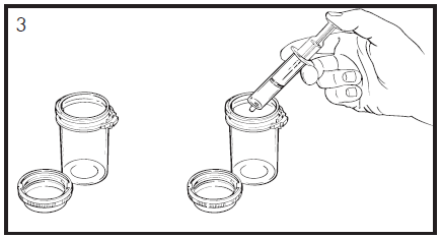
Step 1
- Remove the bottle cap by pushing down while turning the cap anticlockwise (to the left).
- After removing the cap, set the bottle upright on a table-top.
- There is a plastic covered foil seal on the top of the bottle, which must be removed before using the bottle for the first time.
- While holding the bottle in its upright position, insert the press-in-bottle-adaptor into the neck of the bottle. This needs only to be done the first time that the bottle is opened. The adaptor can then be left in the bottle for all subsequent uses



Step 2
- Next, insert the tip of the measuring syringe into the centre opening of the bottle and press down firmly
  While holding the bottle and syringe with one hand, draw up the prescribed dose with the other hand by pulling on the plunger.
  NOTE: Medicine will not flow into the syringe unless you keep the bottle in its upright position

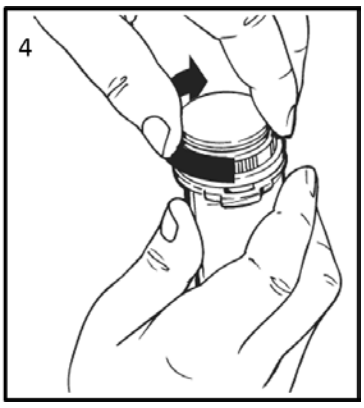


Step 3



- Remove the syringe from the centre opening of the bottle.
- Empty the medicine from the syringe into one of the dosing cups provided by pushing on the plunger Repeat this step for the second dosing cup.
- Then add about 60 ml of water to each dosing cup (60 mL is about 4 tablespoons).

Step 4



- 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 (Caution: as the dosing cup cap is reversible, only after the clicking noise is heard it is ensured that the cap is closed in the child-resistant manner).
- Rinse out the syringe with water.

- Just before going to sleep:
- Adult patients should place the second dose near their bed.
- The parent or caregiver of adolescents and children aged 7 years and over should not leave the second dose near the child's bed or within easy reach of the child.
- You may need to set an alarm so you wake up to take your second dose no earlier than 2½ hours and no later than 4 hours after your first dose.

Then:

- Remove the cap from the first dosing cup by pressing down on the child-resistant locking tab and turning the cap anticlockwise (to the left).
- Drink all of the first dose while sitting in bed, recap the cup, and then lie down right away. For children who sleep longer than 8 hours but less than 12 hours, the first dose may be given after the child has been sleeping for 1 to 2 hours.

- When you wake up or wake up the child 2 ½ to 4 hours later, remove the cap from the second dosing cup. While sitting in bed, drink all of the second dose right before lying down to continue sleeping. Recap the second cup.

If you have the impression that the effect of Xyrem is too strong or too weak, talk to your doctor or pharmacist.

If you take more Xyrem than you should

Symptoms of Xyrem overdose may include agitation, confusion, impaired movement, impaired breathing, blurred vision, profuse sweating, headache, vomiting, decreased consciousness leading to coma and seizures, excessive thirst, muscle cramps and weakness. If you take more Xyrem than you were told to take, or take it by accident, get emergency medical help right away. You should take the labelled medicine bottle with you, even if it is empty.

If you forget to take Xyrem

If you forget to take the first dose, take it as soon as you remember and then continue as before. If you miss the second dose, skip that dose and do not take Xyrem again until the next night. Do not take a double dose to make up for a forgotten dose.

If unsure if you took Xyrem

If in doubt about administration of a dose, do not re-administer the dose to reduce the risk of overdose

If you stop taking Xyrem
You should continue to take Xyrem for as long as instructed by your doctor. You may find that your cataplexy attacks return if your medicine is stopped and you may experience insomnia, headache, anxiety, dizziness, sleeping problems, sleepiness, hallucination and abnormal thinking.
If you stop taking Xyrem for more than 14 consecutive days, you should consult your doctor as you should restart taking Xyrem at a reduced dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. These are usually mild to moderate..

Adults - most common side effects observed in clinical studies (occurring in 10% to 20% of patients):
- dizziness
- nausea
- headache.

If you experience any of these side effects, **tell your doctor straight away.**

Children and adolescents - most common side effects observed in a clinical study:
- bed wetting (18.3%)
- nausea (12.5%)
- vomiting (8.7%)
- weight decrease (8.7%)
- decreased appetite (6.7%)
- headache (5.8%)
- dizziness (5.8%)
- suicidal thoughts (1%)
- feeling mentally unwell (loss of contact with reality) (1%)

If you experience any of these side effects, **tell your doctor straight away**

The side effects in adults and children are the same. If you experience any of the side effects listed below, tell your doctor straight away:

Very common (may affect more than 1 in 10 people):
- nausea
- dizziness
- headache

Common (may affect up to 1 in 10 people):
- sleeping problems including insomnia, abnormal dreams, sleep paralysis, sleepiness, nightmares, sleep walking, bed wetting, excessive daytime sleepiness, difficulty in falling asleep in the middle of the night
- feeling drunk, trembling, confusion/ disorientation, blurred vision, balance disorder, fall, feeling of “spinning” (vertigo),
- feeling the heart beat, increased blood pressure, shortness of breath
- vomiting, stomach pains, diarrhoea
- anorexia, decreased appetite, weight loss
- weakness, tiredness, sedation
- sweating
- depression

- muscle cramps, swelling
- joint pain, back pain
- disturbance in attention, disturbed sensitivity particularly to touch, abnormal touch sensation, abnormal taste
- anxiety, nervousness
- urinary incontinence
- snoring, congestion of the nose
- rash
- inflammation of the sinuses,inflammation of nose and throat

Uncommon (may affect up to 1 in 100 people):
- psychosis (a mental disorder that may involve hallucinations, incoherent speech, or disorganized and agitated behaviour)
- paranoia, abnormal thinking, hallucination, agitation, suicide attempt
- difficulty in falling asleep, restless legs
- forgetfulness
- myoclonus (involuntary contractions of muscles)
- involuntary passage of faeces
- hypersensitivity

Not known (cannot be estimated from the available data):
- convulsion
- decreased breathing depth or rate, short cessation of breathing during sleep
- hives
- suicidal thoughts, delusion, thoughts of committing violent acts (including harming others)
- irritability, aggression
- euphoric mood
- panic attack
- mania / bipolar disorder
- dry mouth, dehydration
- swelling face (angioedema)
- bruxism (teeth grinding and jaw clenching)
- pollakiuria / micturition urgency (increase need to urinate)
- tinnitus (noise in the ears such as ringing or buzzing)
- sleep-related eating disorder
- increased appetite
- loss of consciousness
- dyskinesia (e.g. abnormal, uncontrolled movements of the limbs)
- dandruff
- increased sexual desire
- nocturia (excessive urination at night)
- choking sensation

If you experience any of the side effects listed above, **tell your doctor straight away.**

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Xyrem

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the bottle after (EXP). The expiry date refers to the last day of that month.

After dilution in the dosing cups, the preparation should be used within 24 hours.

Once you open a bottle of Xyrem, any contents that you have not used with 90 days of opening should be disposed of.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Xyrem contains
- The active substance is sodium oxybate. Each mL contains 500 mg of sodium oxybate.
- The other ingredients are purified water, malic acid and sodium hydroxyde.

What Xyrem looks like and contents of the pack
Xyrem is supplied in a 240 mL amber plastic bottle containing 180 mL of oral solution and closed with a child-resistant cap. When the bottle is delivered, there is a plastic covered foil seal which is on the top of the bottle, underneath the cap. Each pack contains one bottle, a press-in-bottle-adaptor (PIBA), a plastic measuring syringe and two dosing cups with child-resistant caps.
Xyrem is a clear to slightly opalescent solution.

Marketing Authorisation Holder
UCB Pharma SA, Allée de la Recherche 60, B-1070 Brussels, Belgium

Manufacturer
UCB Pharma S.A., Chemin du Foriest, B-1420 Braine l'Alleud, Belgium

You should have received a Xyrem Information Pack from your physician, which includes a booklet on how to take the medicine, a Frequently Asked Questions patient information sheet and a patient alert card.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
UCB Pharma SA/NV
Tel/Tél: +32 / (0)2 559 92 00

България
Ю СИ БИ България ЕООД
Тел.: + 359 (0) 2 962 30 49

Česká republika
UCB s.r.o.
Tel: + 420 221 773 411

Danmark
UCB Nordic A/S
Tlf: + 45 / 32 46 24 00

Lietuva
UCB Pharma Oy Finland
Tel: + 358 9 2514 4221 (Suomija)

Luxembourg/Luxemburg
UCB Pharma SA/NV
Tél/Tel: +32 / (0)2 559 92 00

Magyarország
UCB Magyarország Kft.
Tel.: + 36-(1) 391 0060

Malta
Pharmasud Ltd.
Tel: +356 / 21 37 64 36

Deutschland
UCB Pharma GmbH
Tel: + 49 /(0) 2173 48 4848

Eesti
UCB Pharma Oy Finland
Tel: + 358 9 2514 4221 (Soome)

Ελλάδα
UCB A.E.
Τηλ: +30 / 2109974000

España
UCB Pharma, S.A.
Tel: + 34 / 91 570 34 44

France
UCB Pharma S.A.
Tél: + 33 / (0)1 47 29 44 66

Hrvatska
Medis Adria d.o.o.
Tel: +385 (0) 1 230 34 46

Ireland
UCB (Pharma) Ireland Ltd.
Tel: + 353 / (0)1-46 37 395

Ísland
UCB Nordic A/S
Sími: + 45 / 32 46 24 00

Italia
UCB Pharma S.p.A.
Tel: + 39 / 02 300 791

Κύπρος
Lifepharma (Z.A.M.) Ltd
Τηλ: + 357 22 34 74 40

Latvija
UCB Pharma Oy Finland
Tel: + 358 9 2514 4221 (Somija)

Nederland
UCB Pharma B.V.
Tel.: +31 / (0)76-573 11 40

Norge
UCB Nordic A/S
Tel: +45 / 32 46 24 00

Österreich
UCB Pharma GmbH
Tel: +43 (0) 1 291 80 00

Polska
UCB Pharma Sp. z o.o.
Tel.: + 48 22 696 99 20

Portugal
UCB Pharma (Produtos Farmacêuticos), Lda
Tel: + 351 / 21 302 5300

România
UCB Pharma Romania S.R.L.
Tel: +40 21 300 29 04

Slovenija
Medis, d.o.o.
Tel: + 386 1 589 69 00

Slovenská republika
UCB s.r.o., organizačná zložka
Tel: + 421 (0) 2 5920 2020

Suomi/Finland
UCB Pharma Oy Finland
Puh/ Tel: + 358 9 2514 4221

Sverige
UCB Nordic A/S
Tel: + 46 / (0) 40 29 49 00

United Kingdom (Northern Ireland)
UCB (Pharma) Ireland Ltd.
Tel: + 353 / (0)1-46 37 395

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/
<----------