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.

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 sleep disorders.

Posology
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 night 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).

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

Paediatric population
The safety and efficacy of sodium oxybate in children and adolescents aged 0-18 years has not been established. No data are available.

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, patients should eat at least several (2-3) hours before taking the first dose of Xyrem at bedtime. 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. Apnoea and respiratory depression have been observed in a fasting healthy subject after a single intake of 4.5 g (twice the recommended starting dose). 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. 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 a depressive illness and/or suicide attempt should be monitored especially carefully for the emergence of depressive symptoms while taking sodium oxybate. Major depression is contraindicated for use with Xyrem (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.

Sodium intake
Patients taking sodium oxybate will have an additional daily intake of sodium that ranges from 0.82 g (for a 4.5 g/day Xyrem dose) to 1.6 g (for a 9 g/day Xyrem dose). A dietary 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).

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.

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 Xyrem 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 embryolethality 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
It is not known whether sodium oxybate and/or its metabolites are excreted into breast milk. Breastfeeding is not recommended during treatment with sodium oxybate.

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.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions are 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.

The safety and efficacy 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. Additionally, randomised, double-blind, placebo-controlled, crossover drug-drug interaction studies with ibuprofen, diclofenac and valproate were performed in healthy subjects and are summarised in section 4.5.

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

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

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

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

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.

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. 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.

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. However, due to the rapid metabolism of sodium oxybate, these measures are not warranted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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.

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 1 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	Xyrem 4.5 - 9
Trial 2	EDS (MWT)	231	Sleep Architecture/ ESS/CGIc/Naps	8 weeks	Xyrem 6 – 9 Modafinil 200-600 mg
Trial 3	Cataplexy	136	EDS (ESS)/CGIc/Naps	4 weeks	Xyrem 3 - 9
Trial 4	Cataplexy	55	None	4 weeks	Xyrem 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 2 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 3 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 4 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 5 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 6 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.

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.

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

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.

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**:** 40 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 consisting of an LDPE bottle-well housing, a Silastic Biomedical ETR Elastomer valve, an acrylonitrile butadiene styrene terpolymer valve retainer and LDPE tubing, 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 Ltd
208 Bath Road
Slough
Berkshire
SL1 3WE
United Kingdom

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 Ltd
208 Bath Road
Slough
Berkshire SL1 3WE
United Kingdom

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 about the important risks. The four components of this comprehensive program are:

- Healthcare Professional Checklist (i.e. treatment initiation forms): to remind physicians to check the 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.
- Frequently Asked Questions (FAQ) Patient Information Sheet (to be given to the patient): to provide patients with responses to some questions they might have about taking Xyrem.

- How to Take Xyrem brochure (to be given to the patient): to provide patients with information related to the use of Xyrem.
- Patient Alert Card (to be given to the patient): to remind patients, physicians and/or pharmacists 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

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 40 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 Ltd
208 Bath Road
Slough
Berkshire
SL1 3WE.
UK.

12. MARKETING AUTHORISATION NUMBER

EU/1/05/312/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Xyrem 500 mg/mL (applies to carton only)

17. UNIQUE IDENTIFIER – 2D BARCODE

The following statement should be included in this section in grey-shading:
<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.

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;
- 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
Do not give this medicine to children and adolescents.

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 your are taking any of the following types of medicines:

- medicines that increase central nervous system activity and 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

Xyrem with food, drink and 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.

It is not known whether Xyrem passes into breast milk. Patients taking Xyrem should stop breast feeding.

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.

Xyrem contains sodium
You need to monitor the amount of salt you take as Xyrem contains sodium (which is found in table salt) which may affect you if you have had high blood pressure, heart or kidney problems in the past. If you take two 2.25 g doses of sodium oxybate each night you will take 0.82 g of sodium, or if you take two 4.5 g doses of sodium oxybate each night you will take in 1.6 g sodium. You may need to moderate your intake of salt.

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.

The recommended starting dose is 4.5 g/day, given as two equally divided doses of 2.25 g/dose. Your doctor may gradually increase your dose up to a maximum of 9 g/day given as two equally divided doses of 4.5 g/dose.

Take Xyrem orally two times each night. Take the first dose upon getting into bed and the second dose 2.5 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 two-three hours after a meal. Prepare both doses before bedtime. Take doses within 24 hours after preparation.
If you are taking valproate together with Xyrem, the dose of Xyrem will be adapted by your doctor. The recommended starting dose for Xyrem, when used together with valproate, is 3.6 g/day, given as two equally divided doses of 1.8 g. take the first dose upon getting into bed and the second dose 2.5 to 4 hours later.

If you have kidney problems, you should consider a dietary recommendation to reduce sodium intake.

If you have liver problems, the starting dose should be halved. Your doctor may gradually increase your dose.

<u>Instructions on how to dilute Xyrem</u>

The following instructions explain how to prepare Xyrem. Please read the instructions carefully and follow them step by step.

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

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

2. Next, insert the tip of the measuring syringe into the centre opening of the bottle and press down firmly (See Figure 1).

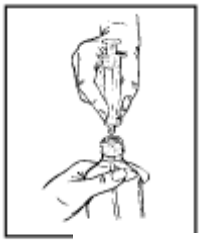

Figure 1

3. 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 (See Figure 2).

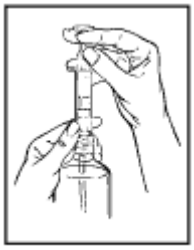

Figure 2

4. 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 (See Figure 3). 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).

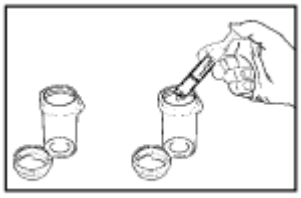

Figure 3

5. 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 4). Rinse out the syringe with water.

Figure 4

6. Just before going to sleep, place your second dose near your bed. You may need to set an alarm so you wake up to take your second dose no earlier than 2.5 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 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.

7. When you wake up 2.5 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. 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 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. If you experience any of these, 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, blurred vision, feeling the heart beat, vomiting, stomach pains, diarrhoea, anorexia, decreased appetite, weight loss, weakness, abnormal dreams, tiredness, feeling drunk, sleep paralysis, sleepiness, trembling, confusion/ disorientation, nightmares, sleep walking, bed wetting, sweating, depression, muscle cramps, swelling, fall, joint pain, back pain, excessive daytime sleepiness, balance disorder, disturbance in attention, disturbed sensitivity particularly to touch, abnormal touch sensation, sedation, abnormal taste, anxiety, difficulty in falling asleep in the middle of the night, nervousness, feeling of "spinning" (vertigo), urinary incontinence, shortness of breath, snoring, congestion of the nose, rash, inflammation of the sinuses, inflammation of nose and throat, increased blood pressure

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, hives, suicidal thoughts, short cessation of breathing during sleep, euphoric mood, dry mouth, swelling face (angioedema), dehydration , panic attack , mania / bipolar disorder , delusion , 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 , loss of consciousness, increased appetite , irritability , aggression, dyskinesia (e.g. abnormal, uncontrolled movements of the limbs) and thoughts of committing violent acts (including harming others).

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 40 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 and Manufacturer

UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE, United Kingdom.

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:

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Lietuva
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UCB Pharma Ltd.
Tel : +44 / (0)1753 534 655

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/
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