

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xyrem 500 mg/ml oral solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml Xyrem contains 500 mg of sodium oxybate.

For 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 cataplexy in adult patients with narcolepsy.

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. Due to the well known potential of abuse of sodium oxybate, physicians should evaluate patients for a history of drug abuse (see section 4.4).

The recommended starting dose is 4.5 g/day sodium oxybate (9 ml Xyrem) divided into two equal doses of 2.25 g/dose (4.5 ml/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 4.5g/dose (9ml/dose) by adjusting up or down in dose increments of 1.5 g/day (i.e. 0.75 g/dose or 1.5 ml/dose). A minimum of two weeks is recommended between dosage increments. The dose of 9g/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).

A 10ml measuring syringe and two 90 ml dosing cups are provided with Xyrem. Each dose of Xyrem must be diluted with 60 ml of water in the dosing cup prior to ingestion.

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

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.

Using Xyrem

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 dosing cup with child resistant cap. Each measured dose of Xyrem must be dispensed into the dosing cup and diluted with 60 ml of water prior to ingestion.

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 medication for more than 14 consecutive days, titration should be restarted from the lowest dose

Patients with hepatic impairment

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

Patients with renal impairment

Patients with impaired renal function should consider a dietary recommendation to reduce sodium intake (see section 4.4).

Elderly patients

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

Paediatric patients

Safety and effectiveness in children and adolescents has not been established, therefore use in patients under 18 years of age is not recommended.

4.3 Contraindications

Hypersensitivity to sodium oxybate or to any of the excipients.

Sodium oxybate is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency.

Sodium oxybate is contraindicated in patients being treated with opioids or barbiturates.

4.4 Special warnings and special precautions for use

Xyrem has the potential to induce respiratory depression

Abuse potential and dependence

The active substance in Xyrem is sodium oxybate, which is as the sodium salt of gamma hydroxybutyrate (GHB), a CNS depressant active substance with well known abuse potential. Physicians should evaluate patients for a history of drug abuse and follow such patients closely.

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.

CNS depression

The combined use of alcohol or any CNS depressant drug with sodium oxybate may result in potentiation of the CNS-depressant effects of sodium oxybate. Therefore, patients should be warned against the use of alcohol in conjunction with sodium oxybate.

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.

Respiratory 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 4.5g (twice the recommended starting dose). Patients should be questioned regarding signs of CNS or respiratory depression. Special caution should be observed in patients with an underlying respiratory disorder. 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 Xyrem should be avoided.

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 psychosis, paranoia, hallucinations, and agitation. The emergence of thought disorders 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.

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 0.75g (for a 4.5g/day (9ml) Xyrem dose) to 1.6g (for a 9g/day (18ml) 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).

Patients with compromised liver function

Patients with compromised liver function will have an increased elimination half-life and systemic exposure to sodium oxybate (see Section 5.2). The starting dose should therefore be halved in such patients, and response to dose increments monitored closely (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.

Childhood and adolescence

Safety and effectiveness in children and adolescents has not been established, therefore use in patients under 18 years of age is not recommended.

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.

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate and protriptyline hydrochloride (an antidepressant), zolpidem tartrate (a hypnotic), and modafinil (a stimulant). However, pharmacodynamic interactions with these drugs have not been assessed.

The co-administration of omeprazole (a drug that alters gastric pH) has no clinically significant effect on the pharmacokinetics of sodium oxybate. The dosage of sodium oxybate therefore does not require adjustment when given concomitantly with proton pump inhibitors.

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).

Since sodium oxybate is metabolised by GHB dehydrogenase there is a potential risk of an interaction with drugs that stimulate or inhibit this enzyme (e.g. valproate, phenytoin or ethosuximide). No interaction studies have been conducted in human subjects

Sodium oxybate has been administered concomitantly with CNS stimulant agents in approximately 80 % of patients in clinical studies. Whether this affected respiration during the night is unknown.

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 events have increased when sodium oxybate is co-administered with tricyclic antidepressants.

4.6 Pregnancy and lactation

Pregnancy

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

There are no adequate data on the use of sodium oxybate during the first trimester of pregnancy. Limited data from pregnant patients during second and third trimester indicate no malformative nor foeto/neonatal toxicity of sodium oxybate.

Sodium oxybate is not recommended during pregnancy.

Lactation

It is not known whether sodium oxybate is excreted into breast milk. Breastfeeding is not recommended when treating with Xyrem.

4.7 Effects on ability to drive and use machines

Sodium oxybate has a 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

The most commonly reported adverse drug reactions are sleep disorder, dizziness, nausea, and headache, all occurring in 10 % to 25 % of patients.

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)

Immune system disorders:

Common: hypersensitivity

Metabolism and nutrition disorders:

Common: anorexia

Psychiatric disorders:

Very common: sleep disorder

Common: abnormal dreams, abnormal thinking, confusion, disorientation, nightmares, sleepwalking, depression, hallucination, agitation

Uncommon: psychosis, paranoia

Nervous system disorders:

Very common: dizziness, headache

Common: sleep paralysis, somnolence, tremor, amnesia

Uncommon: myoclonus, convulsion

Eye disorders:

Common: blurred vision

Respiratory, thoracic and mediastinal disorders:

Rare: respiratory depression

Gastrointestinal disorders:

Very common: nausea (the frequency of nausea is higher in women than men)

Common: vomiting, upper abdominal pain, diarrhoea,

Uncommon: faecal incontinence

Skin and subcutaneous tissue disorders:

Common: sweating, rash

Uncommon: urticaria

Musculoskeletal, connective tissue and bone disorders:

Common: muscle cramps

Renal and urinary disorders:

Common: enuresis nocturna

General disorders and administration site conditions:

Common: asthenia, fatigue, feeling drunk

Investigations:

Common: blood pressure increased

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 events such as insomnia, headache, anxiety, dizziness, sleep disorder, somnolence, hallucination, and psychotic disorders were observed after GHB discontinuation.

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.

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.

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 drug 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 hydroxybutyric acid

Sodium oxybate is a central nervous system depressant with anti-cataplectic activity in patients with narcolepsy. The precise mechanism by which sodium oxybate produces an effect on cataplexy 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 as an anti-cataplectic agent was established in two randomised, double-blind, placebo-controlled trials (Trials 1 and 2) in patients with narcolepsy, 85% and 80%, respectively, of whom were also being treated with CNS stimulants. The high percentages of concomitant stimulant use make it impossible to assess the efficacy and safety of sodium oxybate independent of stimulant use. In each trial, the treatment period was 4 weeks and the total daily doses ranged from 3 to 9 g, with the daily dose divided into two equal doses. The first dose each night was taken at bedtime and the second dose was taken 2.5 to 4 hours later. There were no restrictions on the time between food consumption and dosing.

Trial 1 was a multi-centre, double-blind, placebo-controlled, parallel-group trial that enrolled 136 narcoleptic patients with moderate to severe cataplexy (median of 21 cataplexy attacks per week) at baseline. Prior to randomization, medications with possible effects on cataplexy were withdrawn, but stimulants were continued at stable doses. Patients were randomised to receive placebo, Sodium oxybate 3 g/day, Sodium oxybate 6 g/day, or Sodium oxybate 9 g/day, in divided nightly doses.

Trial 2 was a multi-centre, double-blind, placebo-controlled, parallel-group, randomised withdrawal trial that enrolled 55 narcoleptic patients who had been taking open-label sodium oxybate for 7 to 44 months. To be included, patients were required to have a history of at least 5 cataplexy attacks per week prior to any treatment for cataplexy. Patients were randomised to continued treatment with sodium oxybate at their stable dose or to placebo. Trial 2 was designed specifically to evaluate the continued efficacy of sodium oxybate after long-term use. The primary efficacy measure in each clinical trial was the frequency of cataplexy attacks.

Table 1
Summary of Outcomes in Clinical Trials Supporting the Efficacy of Sodium Oxybate

Dosage	Number of Subjects	Cataplexy Attacks		
		Baseline	Median Change from Baseline	
Trial 1		Median attacks/week		
Placebo	33	20.5	-4	
3.0 g/day	33	20.0	-7	
6.0 g/day	31	23.0	-10	
9.0 g/day	33	23.5	-16	
Trial 2		Median attacks/two weeks		
Placebo	29	4.0	21.0	-
Sodium oxybate	26	1.9	0	

In Trial 1, both the 6 g/day and 9 g/day doses gave statistically significant reductions in the frequency of cataplexy attacks. The 3 g/day dose had no significant effect. In Trial 2, following the discontinuation of long-term open-label sodium oxybate therapy, patients randomised to placebo experienced a significant increase in cataplexy ($p < 0.001$), providing evidence of long-term efficacy of sodium oxybate.

In Trial 2, the response was numerically similar for patients treated with doses of 6 to 9 g/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 but incompletely absorbed after oral administration; absorption is delayed and decreased by a high fat meal. It is eliminated mainly by metabolism with a half-life of 0.5 to 1 hour. Pharmacokinetics are nonlinear with the area under the plasma concentration curve (AUC) versus time curve increasing 3.8-fold as dose is doubled from 4.5g to 9g. The pharmacokinetics are not altered with repeat dosing.

Absorption: Sodium oxybate is absorbed rapidly following oral administration with an absolute bioavailability of about 25 %. 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 (T_{max}) 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 T_{max} increased from 0.75 hr to 2.0 hr) and a reduction in peak plasma level (C_{max}) 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.

Metabolism: Animal studies indicate that metabolism is the major elimination pathway for sodium oxybate, producing carbon dioxide and water via the tricarboxylic acid (Krebs) cycle and secondarily by 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 drug appears in human urine within 6 to 8 hours after dosing. Faecal excretion is negligible.

Special Populations:

Elderly patients: The pharmacokinetics of sodium oxybate in patients greater than the age of 65 years have not been studied.

Paediatric patients: 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 Disease: 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 $t_{1/2}$ of 59 and 32 versus 22 minutes). It is prudent to reduce the starting dose of sodium oxybate by one-half in patients with liver dysfunction (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 drugs. Self-administration studies in rats, mice and monkeys have produced conflicting results, whereas tolerance to GHB as well as cross-tolerance to alcohol have 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 (see Section 4.2), the preparation should be used within 24 hours.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Amber oval PET bottle with a child resistant closure composed of HDPE/polypropylene with a LDPE liner fitted with a PVC tamper evident seal.

Each carton contains one bottle of 180ml Xyrem, a press-in bottle adaptor consisting of an LDPE bottle-well housing, an EPDM rubber valve, an acrylonitrile butadiene styrene terpolymer valve retainer and LDPE tubing, a graduated 10ml measuring device (polypropylene syringe), two polypropylene dosing cups and two HDPE child resistant screw closures.

6.6 Instructions for use and handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

UCB Pharma Ltd
208 Bath Road
Slough
Berkshire
SL1 3WE
UK

8. MARKETING AUTHORISATION NUMBER

EU/1/05/312/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

13/10/2005

10. DATE OF REVISION OF THE TEXT

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER
RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Ashton Pharmaceuticals Limited
Vale of Bardsley, Ashton under Lyne
Lancashire OL7 9RR
United Kingdom

B CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

• **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Xyrem 500 mg/ml oral Solution
sodium oxybate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

500 mg/ml sodium oxybate

3. LIST OF EXCIPIENTS

Purified water
Malic acid
Sodium Hydroxide

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution
One 180 ml bottle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use. Read the package leaflet before use

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Keep the container tightly closed.

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

There are no special storage instructions.

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

Return any unused product to your pharmacy.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma Ltd
208 Bath Road
Slough
Berkshire
SL1 3WE.
UK.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/312/001

13. MANUFACTURER'S BATCH NUMBER

<Batch>

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Xyrem 500 mg/ml oral solution
Oral use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use. Keep out of the reach and sight of children.

3. EXPIRY DATE

<EXP {MM/YYYY}>

4. BATCH NUMBER

<Batch>

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

180 ml of a 500mg /ml sodium oxybate solution

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Xyrem is and what it is used for
2. Before you take Xyrem
3. How to take Xyrem
4. Possible side effects
5. Storing Xyrem
6. Further information

The name of your medicine is Xyrem 500 mg/ml oral solution. The active substance is sodium oxybate. One ml of Xyrem contains 500 mg of sodium oxybate. The other ingredients are purified water, malic acid and sodium hydroxide.

The Marketing Authorisation Holder for Xyrem is:

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

Xyrem is Manufactured by:

Ashton Pharmaceuticals Ltd, Vale of Bardsley, Ashton-under-Lyne, Lancashire, OL7 9RR, United Kingdom.

1. WHAT XYREM IS AND WHAT IT IS USED FOR

Xyrem is supplied as an oral solution in a 180 ml tamper-evident amber plastic bottle. 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.

Xyrem works by consolidating night-time sleep, though its exact mechanism of action is unknown.

Xyrem is used to reduce the number of cataplexy attacks in adult patients with narcolepsy.

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.

Narcolepsy is a sleep disorder that may include attacks of sleep during normal waking hours, as well as cataplexy, sleep paralysis, and hallucinations.

2. BEFORE YOU TAKE XYREM

Do not take Xyrem:

- if you are hypersensitive (allergic) to sodium oxybate or any of the other ingredients of Xyrem
- if you have succinic semialdehyde dehydrogenase deficiency (a rare metabolic disorder)
- if you are being treated with opioids or barbiturate agents

Take special care with Xyrem:

- if you have breathing or lung problems
- 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 are taking other CNS depressants or alcohol

- if you have previously had experience with drug abuse
- if you suffer from epilepsy the use of Xyrem is not recommended
- 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 should not be taken by children.

When you discontinue taking Xyrem you need to follow your doctor's instructions as it may result in side effects e.g. headache, lack of sleep, mood changes and hallucinations.

Taking Xyrem with food and drink:

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

Xyrem is to be taken at a set time well after a meal (two - three hours) as food decreases the amount of Xyrem that is absorbed by your body. Xyrem should be diluted only with water.

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 blood pressure, heart or kidney problems in the past. If you take two 4.5ml doses of Xyrem each night you will take 0.75g of sodium, or if you take two 9ml doses of Xyrem each night you will take in 1.6g sodium. You may need to moderate your intake of salt .

Pregnancy

The effects of Xyrem in pregnant women are not known, and so the use of Xyrem in pregnant women is not recommended. Tell your doctor if you are pregnant or are planning to become pregnant. Xyrem is not recommended during pregnancy unless on the advice of your doctor

Ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding

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

Ask your doctor or pharmacist for advice before taking any medicine.

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.

Taking other medicines:

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, even those you bought without a prescription.

3. HOW TO TAKE XYREM

Always take Xyrem exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are unsure.

The usual starting dose is 4.5 g/day (9 ml/day), given as two equally divided doses of 2.25 g/dose (4.5 ml/dose). Your doctor may gradually increase your dose up to a maximum of 9 g/day (18 ml/day) given as two equally divided doses of 4.5g/dose (9 ml/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 well after a meal (two-three hours). Prepare both doses before bedtime.

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.

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.

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

1. The bottle will contain a tamper-evident seal that will need to be removed before using the bottle for the first time.

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. 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).

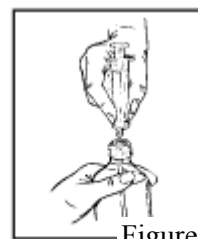


Figure 1

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).

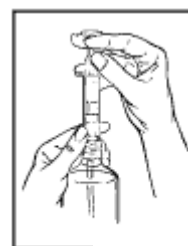


Figure 2

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 mls is about 4 tablespoons)

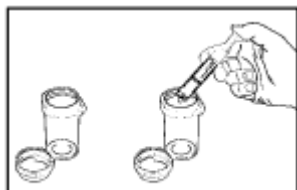


Figure 3

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 forgotten individual doses.

Effects when treatment with Xyrem is stopped:

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.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Xyrem can have side effects. These are usually mild to moderate. If you experience any of these, tell your doctor straight away.

Sodium oxybate has a well known abuse potential. No cases of abuse are known among individuals treated for narcolepsy. However cases of dependency have occurred after the illicit use of sodium oxybate.

Very common side effects include:

Nausea, dizziness, sleeping problems, headache

Common side effects include:

Hypersensitivity, blurred vision, vomiting, stomach pains, diarrhoea, anorexia, weakness, abnormal dreams, abnormal thinking, tiredness, feeling drunk, sleep paralysis, sleepiness, trembling, confusion/disorientation, nightmares, sleep walking, bed wetting, sweating, depression, hallucination, agitation, increased blood pressure, muscle cramps, forgetfulness, rash.

Uncommon side effects include:

Psychosis (a mental disorder that may involve hallucinations, incoherent speech, or disorganized and agitated behavior), paranoia, myoclonus (involuntary contractions of muscles), convulsion, involuntary passage of feces, hives.

Rare side effects include:

Decreased respiratory depth or rate

If any of these affect you severely, tell your doctor.

If you are concerned about any side effect, or if you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. STORING XYREM

Keep out of the reach and sight of children.

Store in the original container.

Do not store Xyrem solutions diluted with water for more than 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 use after the expiry date stated on the bottle.

Return any unused medicine to the pharmacy or ask a pharmacist how to dispose of it. These measures will help to protect the environment.

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

You should have received a Xyrem Information Pack from your physician, which includes a booklet all about Xyrem and a video showing you how to take the product. If you have not received this, please contact the local representative of the Marketing Authorisation Holder, below.

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