SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sodium oxybate Kalceks

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.
Clear to slightly opalescent, colourless to yellowish solution.

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.

Discontinuation of treatment

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 from 0 to 18 years has not been established. No data are available.

Method of administration

Sodium oxybate should be taken orally upon getting into bed and again between 2.5 to 4 hours later. It is recommended that both doses of sodium oxybate should be made up at the same time upon retiring to bed. Sodium oxybate Kalceks is provided for use with a graduated dosing pipette and two 90 ml dosing cups with child resistant caps. Each measured dose of Sodium oxybate Kalceks 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 sodium oxybate at bedtime. Patients should always observe the same timing of dosing in relation to meals. Doses should be taken within 24 hours after preparation (see section 6.3), 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

Sodium oxybate 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 ≥40 kg/m2 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. 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 (see section 4.5).

<u>Abuse potential and dependence</u>

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 sodium oxybate (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 dose) to 1.6 g (for a 9 g/day dose). The maximum daily dose of this product is equivalent to 80% of the WHO recommended maximum daily intake for sodium. Sodium oxybate Kalceks is considered high in sodium. This should be particularly taken into account for those on a low salt diet. 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/day 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 section 4.3).

Antidepressants

Drug interaction studies in healthy adults demonstrated no pharmacokinetic interactions between sodium oxybate (single dose of 2.25 g) and the antidepressants protriptyline hydrochloride (single dose of 10 mg) and duloxetine (60 mg at steady state). No additional effect on sleepiness was observed when comparing single doses of sodium oxybate alone (2.25 g) and sodium oxybate (2.25 g) in combination with duloxetine

(60 mg at steady state). Antidepressants have been used in the treatment of cataplexy. A possible additive effect of antidepressants and sodium oxybate cannot be excluded. The rate of adverse reactions has increased when sodium oxybate is co-administered with tricyclic antidepressants.

Modafinil

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

Omeprazole

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

Ibuprofen

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

Diclofenac

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

GHB dehydrogenase inhibitors

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

The co-administration of sodium oxybate (6 g per day) with valproate (1250 mg per day) resulted in an increase in systemic exposure to sodium oxybate by approximately 25% and no significant change in C_{max}. No effect on the pharmacokinetics of valproate was observed. The resulting pharmacodynamic effects, including increased impairment in cognitive function and sleepiness, were greater with co-administration than those observed with either drug alone. If concomitant use is warranted, patient response and tolerability should be monitored and dose adjustments made if required.

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 (see 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.

Breastfeeding

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

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 summarized 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 (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

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

Infections and infestations

Common: nasopharyngitis, sinusitis

Immune system disorders

Uncommon: hypersensitivity

Metabolism and nutrition disorders

Common: anorexia, decreased appetite
Not known: dehydration, increased appetite

Psychiatric disorders

Common: depression, cataplexy, anxiety, abnormal dreams, confusional state, disorientation, nightmares, sleepwalking, sleep disorder, insomnia, middle insomnia, nervousness

Uncommon: suicide attempt, psychosis, paranoia, hallucination, abnormal thinking, agitation, initial insomnia

Not known: suicidal ideation, homicidal ideation, aggression, euphoric mood, sleep-related eating disorder, panic attack, mania/bipolar disorder, delusion, bruxism, irritability and increased libido

Nervous system disorders

Very common: dizziness, headache

Common: sleep paralysis, somnolence, tremor, balance disorder, disturbance in attention, hypoaesthesia, paraesthesia, sedation, dysgeusia

Uncommon: myoclonus, amnesia, restless legs syndrome

Not known: convulsion, loss of consciousness, dyskinesia

Eye disorders

Common: blurred vision

Ear and labyrinth disorders

Common: vertigo
Not known: tinnitus

Cardiac disorders

Common: palpitations

Vascular disorders

Common: hypertension

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea, snoring, nasal congestion

Not known: respiratory depression, sleep apnoea

Gastrointestinal disorders

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

Common: vomiting, diarrhoea, abdominal pain upper

Uncommon: faecal incontinence

Not known: dry mouth

Skin and subcutaneous tissue disorders

Common: hyperhidrosis, rash

Not known: urticaria, angioedema, seborrhea

Musculoskeletal and connective tissue disorders

Common: arthralgia, muscle, spasms, back pain

Renal and urinary disorders

Common: enuresis nocturna, urinary incontinence

Not known: pollakiuria/micturition urgency, nocturia

General disorders and administration site conditions

Common: asthenia, fatigue, feeling drunk, oedema peripheral

Investigations

Common: blood pressure increased, weight decreased

Injury, poisoning and procedural complications

Common: fall

Description of selected adverse reactions

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

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. Events of hypernatremia with metabolic alkalosis have been reported in the context of concomitant use of NaCl infusion.

Management

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

Although gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid sequence induction (without the use of sedative) should be considered.

No reversal of the central depressant effects of sodium oxybate can be expected from flumazenil administration. There is insufficient evidence to recommend the use of naloxone in the treatment of overdose with GHB. The use of haemodialysis and other forms of extracorporeal medicinal product removal have not been studied in sodium oxybate overdose. 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 night-time 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	Sodium oxybate 4.5 – 9
Trial 2	EDS (MWT)	231	Sleep Architecture/ ESS/CGIc/Naps	8 weeks	Sodium oxybate 6 – 9 Modafinil 200-600 mg

Trial 3	Cataplexy	136	EDS (ESS)/CGIc/Naps	4 weeks	Sodium oxybate 3 – 9
Trial 4	Cataplexy	55	None	4 weeks	Sodium oxybate 3 – 9

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

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

Table 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 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

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

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

After first opening: 90 days.
After dilution in the dosing cups, the preparation should be used within 24 hours.

6.4 Special precautions for storage

Store below 25°C.
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

180 ml of solution in a 200 ml amber PET bottle which is closed with a child resistant closure composed of polypropylene/HDPE tamper evident cap with a polespan inner liner.

Each carton contains one bottle, a press-in bottle LDPE adapter, a graduated dosing pipette (polypropylene/polyethylene), two polypropylene dosing cups with HDPE child resistant screw caps.

6.6 Special precautions for disposal

No special requirements.

7 MANUFACTURER

AS KALCEKS
Krustpils iela 71E, Rīga, LV-1057, Latvia

8 MARKETING AUTHORISATION HOLDER

A.L.Medi-Market Ltd., 3 Hakatif street, Emek Hefer Industrial Park, 3877701

9 MARKETING AUTHORISATION NUMBER

176-49-37378-99

Approved in December 2024