SCIENTIFIC DISCUSSION

1 Quality aspects

1.1 Introduction

Sodium oxybate is a simple molecule, the sodium salt of gamma-hydroxybutyric acid (GHB) and is presented in the form of a stabilised oral solution, 500mg/ml

1.2 Active Substance

Sodium oxybate is the Common Name of the substance butanoic acid 4-hydroxy-monosodium salt. At the time of writing this report there is no INN for this substance.

1.2.1 Manufacture

The manufacturing process is very simple and is basically a one-step hydrolysis of gamma butyrolactone under alkaline conditions with sodium hydroxide.

Starting materials and critical steps are well defined; there are no intermediates.

The active substance is obtained as a white solid which is dried, 'de-lumped' and packed.

The characterisation of the substance arising from the documented method of synthesis confirms that it is indeed sodium oxybate and this has been done by the usual range of spectroscopic methods including UV, IR & NMR together with elemental analysis and pKa determination.

Since sodium oxybate is to be given in solution, polymorphism has not been investigated

1.2.2 Specification

The specification includes test for identification (IR, HPLC), assay (HPLC), related impurities (HPLC) together with tests for water content (KF) residual solvents (GC) and heavy metals, all performed by validated methods. It is not necessary to control solid state properties.

The impurities include a number of named impurities and one un-named impurity, the levels of which have all been qualified on a toxicological basis and are considered to present no unnecessary risk.

Batch analyses (n = 45) from the site of manufacture defined in the dossier, demonstrate satisfactory compliance with the agreed specification and indicate good uniformity.

1.2.3 Stability

In addition to forced degradation studies in the solid state and in solution, stability studies have been performed on 6 batches of sodium oxybate under ICH conditions, accelerated and long term. No significant negative trends or out of specification results were observed in the formal ICH stability investigation, and on the basis of the accumulated results a satisfactory re-test period has been defined.

1.3 Medicinal Product

1.3.1 Pharmaceutical Development

The product is a simple aqueous solution which is stabilised with malic acid (hydroxysuccinic acid) and adjusted to the pH of maximum stability. From a microbiological point of view, investigations on this formulation showed that the product also had intrinsic antimicrobial activity and passed the test for efficacy of antimicrobial preservatives; therefore it was considered unnecessary to include a preservative in the formulation.

The product is presented as a plastic PET bottle with a child-resistant screw cap closure for the liquid, and in order to facilitate accurate dosage a separate dispensing or dosing system is attached at time of first use. This consists of a plastic adaptor to fit into the bottle, leading to a syringe dispenser allowing the patient to withdraw the accurate dose. In addition, two plastic dosing cups are provided with child-resistant closures.

1.3.2 Manufacture of the Product

The active substance is dissolved in purified water and the pH adjusted with malic acid before dilution with purified water, filtration, and bottling. The validation of this simple scheme was not problematical.

1.3.3 Product Specification

The product release specification includes relevant tests and limits for physical examination, identity

(HPLC & IR), assay (HPLC), impurities (degradation products, HPLC), volume in container, reproducibility of dosage, pH, microbiological attributes (PhEur), etc. Control of rheological properties is not considered necessary for a mobile liquid dosage form.

Batch analyses (n = 18) indicate satisfactory compliance with the agreed specification and satisfactory product uniformity

1.3.4 Stability of the Product

In all, ten batches of product have been investigated for stability under ICH conditions, accelerated and long term, and in all cases the results support the shelflife and storage conditions as defined in the SPC.

In addition, since this is a multidose product with a special adapter and dosing system, additional studies were performed with these plastic components in place, in order to mimic the in-use situation, and a suitable in-use shelflife has been defined.

In general the studies show that the plastic adapter and dosing system is compatible with the solution and does not encourage degradation.

Apart from the physical chemical analytical studies carried out during the stability investigations, microbiological studies were also performed with satisfactory results.

1.4 Discussion on chemical, pharmaceutical and biological aspects

The simple synthesis and manufacture of the product are described and controlled in a relevant manner, and the specifications of the active substance and medicinal product are considered to be relevant for a product of this type. The stability of the product has been well-investigated, both in the unopened form, and with the adaptor and dosing system in place during use.

Satisfactory uniformity of dose has been demonstrated, and there are no unresolved quality issues that could have an impact on the benefit/risk balance for the patient.

2 Non-clinical aspects

2.1 Introduction

2.2 Pharmacology

2.2.1 Primary pharmacodynamics (in vitro/in vivo)

Oxybate (GHB) is a metabolite of γ-aminobutyric acid (GABA) which is synthesised and accumulated by neurones in the brain. It is present at μM concentrations in all brain regions investigated as well as in several peripheral organs, particularly in the gastro-intestinal system. Neuronal depolarisation releases GHB into the extracellular space in a Ca2+-dependent manner. A family of GHB receptors in rat brain have been identified and cloned and most probably belong to the G-protein-coupled receptors. High-affinity receptors for GHB are present only in neurones, with a restricted specific distribution in the hippocampus, cortex and dopaminergic structures of rat brain.

In general, stimulation of these receptors with low (physiological) amounts of GHB induces hyperpolarisation in dopaminergic structures with a reduction of dopamine release. However, in the hippocampus and frontal cortex, GHB seems to induce depolarisation with an accumulation of cGMP and an increase in inositol phosphate turnover. However, at higher (therapeutic) exposures, GHB

receptors are saturated and probably de-sensitised and down-regulated. Such GHBergic potentiations induce dopaminergic hyperactivity, strong sedation with anaesthesia and EEG changes that are consistent with normal sleep and/or epileptic spikes.

The pathogenesis of narcolepsy is still unknown, but an imbalance between monoamines and acetylcholine is generally accepted. Recent research has found a marked reduction of the neuropeptide hypocretin type 1 in the cerebrospinal fluid of a majority of patients and a global loss of hypocretins in post-mortem brain tissue of narcoleptic subjects. The hypocretins are synthesised by a small group of neurones predominantly located in the lateral hypothalamic and perifornical regions of the hypothalamus. The hypothalamic system directly and strongly innervates and potently excites noradrenergic, dopaminergic, serotoninergic, histaminergic and cholinergic neurones. The effect of GHB on this system has not been investigated. However, the available data indicate that its mode of action is likely to relate to non-specific dopaminergic stimulation rather than the hypocretin system.

Formal nonclinical pharmacology studies to investigate the primary pharmacodynamics have not been conducted by the applicant, rather a comprehensive review of the scientific literature has been conducted. The publications included have been selected based on their relevance to the proposed indications, based on evidence of efficacy from early clinical studies. In addition, animal models of cataplexy and narcolepsy are continuing to be developed, but have not yet been fully validated. Little nonclinical information is available on its effects on narcolepsy in general, and cataplexy in particular. Available, directly relevant data, from the published literature, has been reviewed but the current understanding of the role of GHB in the CNS does not provide a mechanistic explanation of the positive clinical effects reported in the dossier. GHB had no effect on cataplexy in dogs with hereditary narcolepsy when administered as a single dose of 500 mg/kg i.v. or 50 mg/kg/day p.o. for 3 consecutive days. However, although such dogs have a mutation of the type 2 hypocretin receptor, the clinical relevance of this model remains to be established. Moreover, a dose of 75 mg/kg/day for at least 14 days is required for efficacy in humans.

Though the precise mode of action is unknown, the sedative properties of GHB and its effects on sleep may play a role in the efficacy observed in humans.

Evidence from a human clinical study (Study OMC-SXB-20) where GHB was administered to narcoleptic patients and overnight polysomnograms (PSG) were recorded, suggests that GHB modifies sleep architecture, specifically a dose-related increase in Stage 3 & 4 slow wave sleep (SWS, delta sleep). The cause of human narcolepsy and cataplexy is, as yet, unknown. Recent evidence points to the loss of hypocretin-containing neurones, possibly due to autoimmune attack, as a likely cause (Scammell 2003). Hypocretin is a neurotransmitter that has roles amongst others, in sleep-wake regulation. Alterations in hypocretin neurotransmission have also been observed in mouse and dog models of narcolepsy, although no studies have been undertaken with GHB in these models. Animal models of cataplexy and narcolepsy are continuing to be developed (Gerashchenko et al, 2003), but the effects of GHB in these models, have yet to be investigated.

2.2.2 Secondary pharmacodynamics

Published literature reports are presented that discuss the potential for effects on the respiratory, cardiovascular, gastrointestinal, renal and endocrine function, together with relevant findings from the toxicology studies.

GHB may increase growth hormone secretion, but this effect is inconsistent across species and dose levels. GHB has no other relevant secondary pharmacodynamic effects in animals.

GHB consistently decreases respiration by effects on minute volume and respiratory rate, with younger animals being more susceptible to these effects. In halothane-anaesthetized rats, GHB (187.5-750 mg/kg i.p.) dose-dependently decreased basal minute volume and respiratory rate compared to pre-injection control, with a maximum decrease to about 60% of pre-injection values for each parameter at the highest dose of GHB (Hedner *et al*, 1980).

Effects on cardiovascular parameters were also studied as part of the repeat dose toxicology studies in dogs, including heart rhythm and P-QRS-T complexes determined from ECGs, and there was no evidence of any dramatic changes in these parameters during the studies at doses up to 600 mg/kg/day (corresponding to male and female AUC0-24 of 3363.05 and 3631.35 µg·hr/mL and Cmax of 583.0

and 726.7 µg/mL). Additionally, in several human clinical studies, there were no significant effects of GHB administration on ECGs. The applicant claims that given the relatively long established clinical use of GHB, as an anaesthetic and sedative and other uses such as for the treatment of alcohol withdrawal, the undesirable effects and risk potential of GHB are well known, and additional nonclinical safety pharmacology studies are not justified. Results of some studies indicate weak rewarding effects and possible development of tolerance in rats and mice, however there is no compelling evidence that GHB represents a significant drug dependence hazard. Interaction of GHB with ethanol and other central nervous system depressants generally result in greater central depressant effects than seen with either drug alone. Numerous case reports of GHB poisoning demonstrate that overdosing in humans is associated with many of the same signs and symptoms as in animals: a rapid onset of drowsiness, nausea, vomiting, myoclonic seizures, respiratory depression progressing to apnoea, and coma.

2.2.3 Safety pharmacology

The applicant has not conducted animal safety pharmacology studies. However, there is ample evidence in the published literature that GHB is a potent CNS depressant, may cause convulsions and potentially fatal respiratory depression and cardiac failure.

On the basis of available information, the lack of conventional safety pharmacology studies is considered acceptable. However, since co-medication is probable, the effects of GHB on respiratory pattern in the presence of other CNS depressing agents like ethanol, and inhibitors of GHB metabolism like valproic acid and ethosuximide are mentioned in the SPC.
A weak tolerance to GHB administration has been demonstrated in a number of specific animal behavioural studies and also the development of cross-tolerance between GHB and ethanol. Therefore, potentially, an acute toxic effect (e.g. acute respiratory depression) could be experienced after drug intake following a period of drug withdrawal, sufficient for the disappearance of tolerance. Caution is advised if treatment is re-started after discontinuation. (SPC, section 4.2). Clinical data (open label study OMC-GHB-3) have failed to show any major development of tolerance on efficacy and the AUC after 8-weeks compared to the first dose was not significantly increased (study OMC-SXB-10, see clinical section). However, as these clinical data are too limited to draw firm conclusions, the potential for development of tolerance, especially with concomitant intake of ethanol, cannot be excluded and is mentioned in the SPC.

2.2.4 Pharmacodynamic drug interactions

Formal studies of pharmacodynamic drug interactions have not been conducted. According to the published literature, concomitant administration of GHB and other CNS depressants (benzodiazepines, barbiturates, alcohol) results in an additive increase in sedation.

2.3 Pharmacokinetics

The applicant has not conducted animal PK studies, with the justification that the more relevant pharmacokinetic data are derived from human exposure. Some data have been compiled from a review of the published literature. Data on non-clinical absorption, distribution, metabolism, and excretion have been compiled from a review of the published literature

2.3.1 Absorption- Bioavailability

In the rat, oral bioavailability was about 50-80%. Kinetics was non-linear, with oral dose increments resulting in an under-proportional increase in Cmax and an over-proportional increase in the AUC. By contrast, i.v. administration resulted in an over-proportional increase in Cmax. Thus, both absorption from the gut and elimination may depend on saturable mechanisms. Saturable absorption from the gut was confirmed in an everted rat intestine model.

2.3.2 Distribution

Whole-body autoradiography following i.v. injection of ^{14}C-GHB in mice showed a fairly uniform distribution pattern of radioactivity due to GHB and/or its metabolites. Shortly after injection, lower radioactivity was found in fatty tissues such as thymus, brown fat, and the white and grey brain matter

than in other tissues, including plasma. However, by 30 minutes after injection, radioactivity was distributed throughout the body, including brain, skeletal muscle, myocardium, kidney, spleen, liver, lung, thymus, urinary bladder, stomach, intestines, and, in pregnant mice, the foetus. GHB distributed rapidly to the brain of rats, dogs and monkeys, producing brain concentrations several orders of magnitude above the physiological level. In the dog, the highest concentration was found in the white matter of the temporal lobe. There are no data on plasma protein binding in animals, but this is likely to be negligible.

2.3.3 Metabolism (in vitro/in vivo)

Metabolism of GHB is rapid and complete and proceeds via succinic semialdehyde, succinate and the Krebs cycle or through γ-hydroxybutyrate and β-oxidation.

The potential for inhibition of CYP isozymes was tested in pooled human liver microsome fractions using standard markers for CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A. In all cases, the IC50 was > 3000 µM (> 378 µg/ml). Since the average maximum human exposure is 142 µg/ml, GHB is not expected to show pharmacokinetic interactions with drugs metabolised by these isozymes. Non P450 mediated effects on GHB metabolism are unclear.

A rat study found that co-administration of compounds stimulating or inhibiting GHB dehydrogenase were able to decrease or increase plasma levels of GHB by up to 1/3. The interactions resulting from the stimulation or inhibition of GHB dehydrogenase, namely with anticonvulsivant drugs and L-dopa are considered to be clinically relevant and are mentioned in the SPC.

2.3.4 Excretion

Clearance is predominantly by biotransformation, with limited amounts of unchanged drug recovered from the urine or faeces. Radiospirometric studies in rats showed that 14C-GHB was rapidly converted to exhaled CO2 and about 2/3 of the dose was excreted by respiration within 6 hours and an additional 10- 20% over the next 18 hours. After oral administration of 14C-labelled GHB (200 mg/kg) to rats, the urinary recovery over 48 hours was 5.5% of the radioactive dose, and only 1.5% was recovered in the faeces. There are no data on the excretion of GHB in the milk of lactating animals. The proposed SPC contains an appropriate statement to this effect.

T½ in rats following oral administration of a single dose of 200 mg/kg was 0.75 h for the α- and 2.68 h for the β-phase. Similar T½ values were observed in dogs and monkeys. In rats, Cmax and AUC values tended to be higher in females than in males, whereas the opposite applied to dogs.

The applicant has been asked to discuss the comparative pharmacokinetics in humans and experimental animals and the implications for a critical appraisal of the relevance of the main species used in the toxicity testing for human safety assessment. In summary, the rat and dog showed similar pharmacokinetic characteristics, although exposure measured as AUC was higher in human than in either rat or dog at the NOAEL. The exposures measured in the maximum tolerated dose toxicokinetic studies (conducted in support of mouse and rat carcinogenicity studies) were, however, greater than in human subjects (Cmax 2.60- and 2.76-fold; AUC 1.21- and 1.64-fold for mouse and rat, respectively).

2.4 Toxicology

All toxicology studies were conducted by the applicant with the exception of data from literature for single dose toxicity and carcinogenicity in mice.

2.4.1 Single dose toxicity

Formal single dose toxicity studies were not conducted. A review of published literature data identified a number of references providing LD50 values in several species. In the mouse, LD50 values of 2960 – 3700 mg/kg following i.p. injection were identified; in the rat, LD50 values were 9990 mg/kg following p.o. administration, and 1700 mg/kg following i.p. injection. In the rabbit and dog, LD50 values in excess of 1000 mg/kg were reported following i.v. administration, which could be increased to over 7000 mg/kg with artificial respiration without lethality.

2.4.2 Repeat dose toxicity (with toxicokinetics)

Repeat-dose toxicity studies comprised 3- and 6-month toxicity studies in rats and 3- and 12-month studies in dogs. Treatment-related clinical signs were mainly related to sedation, reduced food consumption and secondary changes in body weight, body weight gain and organ weights.

In rats, the only treatment-related clinical chemistry changes were a slight reduction of serum albumin and WBC in rats that may have been related to changes in nutritional status. The lowest NOAEL value was 350 mg/kg/day in rats (AUC ≈200 µg.h/ml) based on bodyweight changes.

In dogs, three repeat dose studies have been conducted, an initial rising dose study, followed by 90 day and 52 week exposure studies. In the rising dose study single doses ranging from 150 – 1800 mg/kg/day were investigated, followed by a 5 day continuous dosing phase at 600 mg/kg/day. Treatment related clinical signs included emesis following dosing at 600 mg/kg and 1200 mg/kg and emesis, hypersalivation, ataxia and hypoactivity following the 1800 mg/kg dose. Emesis and ataxia were also observed during the 600 mg/kg/day daily dosing phase. Plasma concentrations were observed to increase in approximate proportion to increasing dose, with emesis leading to decreased plasma concentrations. These signs subsided after the first few weeks of the study, and led to the decision to increase the high dose to 900 mg/kg/day at Week 32. Following this dose increase, similar clinical signs were noted in the 900 mg/kg/day dose group.

There were no treatment-related clinical chemistry, ophthalmology or ECG findings. Necropsy findings included a dark area on the ileal mucosa of one animal, as a result of emesis during the study. A dose-dependent atrophy of the salivary and submucosal oesophageal glands was observed. Such changes are not uncommon with drugs acting on the parasympathetic nervous system. The NOAEL value was 150 mg/kg/day (AUC ≈300 µg.h/ml) based on bodyweight changes and salivary gland atrophy.

The toxicokinetic parameters (mean values calculated from male and female data, since no apparent gender difference has been reported) at the NOAEL and/or NOELs in the repeat dose toxicology studies in rats and dogs are presented in the next table, together with pharmacokinetic parameters for humans from a study where the highest proposed dose of GHB was administered (2 x 4.5 g, 4 h apart, Study OMC-SXB-9).

Species (Study)	Dose	C_{max} (µg/ml)	T_{max} (h)	$T_{½}$ (h)	AUC_{0-t} (µg.h/ml)
Human (OMC-SXB-9)	2 x 4.5g:				
	Dose 1	77.6	1.17		
	Dose 2	142	0.72	0.83	518
Rat 90 day (CHV 2729-106)	350 mg/kg/day[1]	146.5	0.5		205.0
Rat 26 week (Covance 6627-117)	350 mg/kg/day[1]	133.25	0.75		188.9
Dog 90 day (CHV 2729-107)	350 mg/kg/day[2]	314.85	1.06		1022.2
Dog 52 week (Covance 6627-118)	150 mg/kg/day[2]	158.5	0.875	0.99	286.3

[1] NOAEL [2] NOEL

At the NOAEL observed in both rat repeat dose toxicology studies, mean AUC and Cmax values were approx 0.5 fold the values in humans. After the second 4.5 g dose in humans, the Cmax values for rats and humans were approximately the same. At the lowest NOEL for dogs, observed in the dog 52 week toxicology study (150 mg/kg/day), the exposure margin for AUC was approximately 0.5 fold the values observed in humans. The exposure margin for Cmax was approx 0.5 fold the value following the first dose in humans and approximately the same following the second dose in humans. Thus, with the exception of Cmax values following the second GHB dose in humans, exposure to GHB in both rats and dogs was less than observed for humans at the highest proposed therapeutic dose.

2.4.3 Genotoxicity in vitro and in vivo

Genotoxicity studies in vitro (bacterial mutation assays in salmonella and E.coli and chromosomal aberrations in CHO cells in absence and presence of metabolic activation) and in vivo (rat

micronucleus test) did not identify a cause for concern. Sodium oxybate may be considered as non-genotoxic.

2.4.4 Carcinogenicity (with toxicokinetics)

There is available data on rat and mouse with γ-butyrolactone (GBL which converts in GHB rapidly in the body) in two NTP (National Toxicology Program) studies and with sodium oxybate in rats (applicant-sponsored 2-year study). In the rat carcinogenicity study the active substance was administered as sodium oxybate (maximum dose 1000 mg/kg). In the National Toxicology Program mouse carcinogenicity study (CAS No. 96-48-0) the active substance was administered as GBL (maximum dose 525 mg/kg). Provided that no toxicokinetic data was included in the NTP studies, single dose and 14 day dose bridging studies were conducted by the applicant in both rat and mouse to estimate the exposure in these species following administration of sodium oxybate or γ-butyrolactone (GBL) in support of these carcinogenicity studies. The exposures in rat and mouse at the doses corresponding to the maximum doses in the respective carcinogenicity studies was compared to the exposures in humans at the maximum recommended dose of 9g, administered as two 4.5g doses 4 hours apart (OMC-SXB-9). The animal/human exposure ratios for C_{max} were 2.60 and 2.76 for mouse and rat, respectively. Similarly the animal/human exposure ratios for AUC were 1.21 and 1.64 for mouse and rat, respectively. It is not clear whether data from short-term administration (up to 14 days) is informative regarding the exposure of animals at the end of the study, provided that accumulation seemed to occur at least at high doses, as suggested by comparative toxicokinetic analysis of the values obtained in repeated dose studies in rats and dogs. Underestimation of exposure may therefore be given in the bridging studies.

GBL 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. With GBL a non-significant increase of hyperplasia of adrenal medulla was observed also in rats, which poses the possibility of a drug-related effect in both species. Decreased incidence of several neoplasm types in mice (hepatocellular tumors) and rats (mammary fibroadenomas) administered with GBL were also observed in the NTP study.

In rats, both sodium oxybate (applicant-sponsored study) and GBL were classified as non-carcinogenic. In the oxybate study 2/50 pituitary carcinomas were observed in high-dose female rats compared to 0/50 in all other groups including controls. However, this finding was of doubtful statistical significance and the incidence was at the upper bound of historical controls. Since GHB was non-genotoxic and the pituitary carcinomas in the rat were of marginal statistical significance, there is sufficient information to assume that Xyrem is unlikely to be a potential carcinogen in humans. The safety ratios calculated against predicted human exposure were still low but new studies do not seem necessary as no concern has been raised from the available toxicological data.

2.4.5 Reproductive and developmental studies

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. As there are no PK data in pregnant animals, the corresponding exposure margin, calculated from non-pregnant animals is 1.64 times the human one.

In rabbits, foetotoxicity was slight and did not reach statistical significance. The only notable abnormality was hydrocephalus in two foetuses from the same litter in a mid-dose female. Based on historical data provided and taking into consideration that there were no similar findings in any other litter or dose group, this finding was considered to be unrelated to treatment. The rabbit study included toxicokinetics. The highest Cmax recorded was 454 μg/ml, which is 3-fold higher than the predicted human value.

GHB had no adverse effects on the F0 animals in a conventional Segment III study in rats, except for an increase in the incidence of post-dose sedation, low bodyweight gain and reduced food consumption in the high-dose group. Perinatal mortality was increased and mean pup weight was decreased during the lactation period in high-dose F1 animals. Though not dose related, a relationship of these mortalities with the treatment cannot be ruled out. GHB is not to be recommended during pregnancy or breast-feeding and this is reflected in the SPC.

2.4.6 Other toxicity studies

Immunotoxicity studies were not carried out. However, there were no signals of direct immunotoxicity in any of the repeat-dose toxicity studies.

Dependance studies
GHB is a known substance of abuse and in the United States the use of Xyrem is subject to a rigid risk management program. The applicant did not conduct specific animal tests for dependence. However, a review of the published literature was carried out to collect information on the effects of GHB in models of drug discrimination, self-administration and tolerance. 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. However, the characteristics of these effects differ with dose, suggesting the involvement of multiple receptor systems with varied affinities for GHB. Self-administration studies in rats, mice and monkeys have produced conflicting results, whereas tolerance to GHB as well as cross-tolerance to alcohol has been clearly demonstrated in rodents.
The data generated in the file does not allow evaluation of the potential of sodium oxybate to induce withdrawal phenomena. The literature review suggest that mild effects could occur in mice and rats after frequent daily administration and in primates after continuous long term administration (more than 30 days) of 750mg/kg/day dose. The potential for withdrawal seems therefore to exist, though limited. This is reflected in the SPC and will be further evaluated clinically as a post-marketing commitment.

2.5 Environmental risk assessment

A formal environmental risk assessment has not been carried out. It is nevertheless agreed that sodium oxybate is unlikely to pose any perceivable risk to the environment.

2.6 Discussion on the non-clinical aspects

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. The cause of human narcolepsy and cataplexy is, as yet, unknown. Recent evidence points to the loss of hypocretin-containing neurons, possibly due to autoimmune attack, as a likely cause. Animal models of cataplexy and narcolepsy are continuing to be developed, but the effects of GHB in these models, have yet to be investigated.

In addition to its sedative properties, GHB is a potent CNS depressant and may increase growth hormone secretion. The potential for acute respiratory depression after reintroduction of treatment in patients who might have developed tolerance is mentioned in the SPC (4.2) as well as a warning in case of concomitant administration with other CNS depressant, and especially alcohol. (SPC, 4.4 and 4.5)

The interactions resulting from the stimulation or inhibition of GHB dehydrogenase, namely with anticonvulsivant drugs and L-dopa are considered to be potentially relevant in the clinic and are mentioned in the SPC.(section 4.5 and 5.3).

The bioavailability in rats is about 50-80% and the clearance is rapid ($T½ \approx 1h$) with extensive biotransformation which is not P450 dependant. The kinetic is non-linear, due to saturable mechanisms of both absorption and elimination resulting in reduced Cmax and increased AUC from linearity with increasing doses. As GHB is metabolised by γ hydroxybutyrate (GHB) dehydrogenase, there is a potential interaction with drugs that inhibit this enzyme. This is reflected in the SPC (sections 4.5 and 5.3)

In repeat-dose toxicity, treatment-related clinical signs were mainly related to sedation. Safety margins, based on body weight changes and salivary gland atrophy, are low or non-existent. This is in accordance with the frequent occurrence in humans of adverse effects such as nausea, anorexia and parasympathetic disorders (blurred vision, enuresis and sweating).

GHB is non-genotoxic and not considered to present a carcinogenic risk to humans.

In reproductive toxicity studies, foetoxicity was observed in rats and rabbits. The use of GHB is not recommended during pregnancy or breast-feeding and this is reflected in the SPC.

Tolerance to GHB as well as cross-tolerance to alcohol has been clearly demonstrated in rodents. The potential of GHB to induce withdrawal phenomena, demonstrated in animal models, is low, and the relevance for humans will be monitored in the future during the post-authorisation phase.

3 Clinical aspects

3.1 Introduction

Sodium oxybate is directed to the treatment of cataplexy in narcolepsy which is an orphan disease and the development plan reflects this status. The database is small and the claims are supported by studies that in part were conducted on the initiative of the investigators. The sponsor put particularly efforts in one main pivotal study which is of reasonable size with more than 100 patients enrolled.

All analytical methods used were validated. An overview of the pharmacological studies is given in the following table:

Protocol Code	Design	Subject	Dose of GHB	Objectives	Analytical method
OMC-SXB-11	Single-centre, open label, two period, two treatment, crossover, randomised design	36 included, 34 completed. Two dropout due to adverse events. All healthy women.	Single doses GHB. 4.5 g, After an overnight fast or 10 min after a high fat meal.	Study the pharmacokinetics of a single oral dose of Xyrem after a standard high fat meal and after an overnight fast.	LC/MS/MS* (GHB).
OMC-SXB-09	Single centre, open label, two period, two treatment crossover randomised trial.	Three female and 10 male Caucasian, 19 – 47 years of age and 61-90 kg in weight.	Two doses GHB. 2x2.25 g or 2x 4.5 g. First dose administered 2 hours after evening meal and second dose after additional 4 hours.	To study the pharmacokinetics and dose proportionality of Xyrem.	LC/MS/MS* (GHB).
OMC-SXB-08	Single centre, single dose, open label	Healthy subjects. 18 males and 18 females.	Single doses GHB. 4.5 g, Dose administered 2 hours after an evening meal.	To study the pharmacokinetics of GHB in healthy male and females.	LC/MS/MS* (GHB).
OMC-SXB-16	Blinded, placebo controlled	Healthy Subjects (Orphan Medical Inc. Staff.) 6 male and 6 female (age 22 – 55 years)	Single dose GHB (3.0 g). Oral solution swilled in mouth	To compare 3 placebo solutions with active solution with regard to taste.	(Not relevant since all patients expelled GHB solution)
OMC-GHB-04	Open label	Narcoleptic patients maintained on chronic treatment. 4 male and 2 female.	Two doses GHB. Total dose of 6 g (2x3 g, 4 hours apart). A meal was taken 3 hours before the first dose.	To assess PK in patients on chronic treatment.	Gas Chromatography with mass selective detector.
OMC-SXB-10	Open label, two period study.	Narcoleptic patients. 10 women and 3 men (age 23 –52).	Single dose GHB. 4.5 g. A meal was served about 2 hours before dosing.	To assess PK of the initial single dose of GHB and of a single dose after 8 weeks of treatment in narcoleptic patients who had not	LC/MS/MS* (GHB).

Protocol Code	Design	Subject	Dose of GHB	Objectives	Analytical method
				previously received sodium oxybate.	
OMC-SXB-12	Open label, three period, three-treatment, randomised crossover study.	Healthy Subjects 5 female and 10 male (age 19 – 51)	Single doses GHB (3.0 g) and zolpidem 5 mg alone and together after an overnight fast.	To assess any PK interaction between sodium oxybate and zolpidem	LC/MS/MS* (GHB). Liquid Chromatographic with Fluorescence Detector (Zolpidem)
OMC-SXB-14	Open label, three period, three-treatment, randomised crossover study.	Healthy Subjects 5 male, 7 female	Two doses of GHB (2x2.25 g, 4 hours apart) and protriptyline (10 mg), alone and together. Doses were administered 2 hours after a light breakfast.	To assess any PK interaction between sodium oxybate and protriptyline	LC/MS/MS* (GHB). Chromatographic with Fluorescence Detector (Protriptyline)
OMC-SXB-17	Open label, three period, three-treatment, randomised crossover study.	Healthy Subjects 6 female and 7 male. (age 19 – 51)	Single doses of GHB (4.5 g) and modenafinil (200 mg), alone and together after an overnight fast.	To assess any PK interaction between sodium oxybate and Modafinil	LC/MS/MS* (GHB). Liquid chromatographic with absorbance detection (modafinil).
OMC-SXB-24	Open label, three period, three-treatment, randomised crossover study.	Healthy Subjects 20 male 24 female (age 18 – 50)	Single doses of GHB (3 g) prior to and after omeprazole 40 mg once daily for 5 days. Doses were administered 4 hours after the evening meal.	To determine the effect of sub-chronic omeprazole on absorption of oxybate.	LC/MS/MS* (GHB).

*High performance liquid chromatographic (HPLC) with tandem mass spectroscopy (LC/MS/MS)

3.2 Pharmacokinetics

The following pharmacokinetic characteristics of sodium oxybate can be described as follows:

3.2.1 Absorption and Bioavailability/Bioequivalence

Xyrem is presented as an oral solution (500 mg/ml). As sodium oxybate is highly soluble and all the formulations used in the clinical trials were solutions with no excipients except for pH adjustment, no formulation effect is thus expected. Therefore the absence of bioequivalence studies is acceptable.

Sodium oxybate was rapidly absorbed following oral administration in solution. The mean /median time to achieve peak plasma concentration (Tmax) ranged from around 0.5 to 1.25 hours in both healthy volunteers and patients with narcolepsy.

Absolute bioavailability was not studied to avoid potential safety issues following intravenous administration. In the literature, limited data suggest a bioavailability of 27%. This low figure is probably due to a high first pass metabolism.

Influence of food
A clear effect of food on the absorption of sodium oxybate was demonstrated in study OMC-SXB-11. Food intake reduces Cmax by 59%, AUC by 37% and variability in both parameters as well. Administration after a high fat meal showed a slower absorption, resulting in a longer Tmax (2 hours) compared with administration after an overnight fast (0.75 hours). It is considered unlikely that these

small differences in Tmax may have any clinical impact. However, as the concentration/response relationship has not been well established, it is recommended that the proposed posology closely follows what has been used in the clinical trials and that patients should observe the same timing of dosing in relation to meals and upon retiring to bed.

3.2.2 Distribution

Palatini and colleagues (1993) showed that there was essentially no plasma protein binding (<1%) in their study of one volunteer at pre-dialysis concentrations of 3, 10, 20, 100, 200 and 300 mg/ml.

In study OMC-SXB-11, the apparent volume of distribution tended to be higher after the high fat meal than in the fasted situation (Vz/F was 26.9 L and 13.4 L respectively, as referred to 70 kg with rsd% of 84.4% and 101% respectively). The large variability is probably due to the absolute bioavailability factor (F).

3.2.3 Elimination

GHB is eliminated via two metabolic pathways: beta-oxidation and TCA cycle. Renal excretion is negligible (3 to < 10%). Half-life ranges from 0.57 to 0.83 h with an average rsd% of 33.3% across all studies. Total clearance (Cl/F ml/min/kg) ranges from 2.51 to 5.07 with an average rsd% of 25.9% across all studies.

The main PK parameters are summarised in the next 2 tables:

Summary of Pharmacokinetic parameters of GHB in Healthy Volunteers

Study (country)	Subjects entered/ completed males/females	Treatment		Mean (SD) PK parameters (median if no SD shown)			
				Cmax (ug/ml)	Tmax (h)	T½ (h)	$AUC_{0\text{-}inf}$ (ug.h/ml)
OMC-SXB-9 (US)	13/12 10/3 29 y (19-47)	2 x 2.25 g(4h apart)	Dose 1	26.6 (8.6)	0.85 (0.36)	0.59 (0.13)	138 (49.8)
			Dose 2	60.1 (17.5)	0.64 (0.31)		
		2 x 4.5 g (4h apart)	Dose 1	77.6 (24.4)	1.17 (0.54)	0.83 (0.19)	518 (195)
			Dose 2	142 (49.3)	0.72 (0.45)		
OMC-SXB-8 (US)	36/36 18/18 30 y (18-55)	4.5 g	Men	88.3 (21.4)	1.00	0.65 (0.23)	241 (81.7)
			Women	83.0 (18.7)	1.00	0.61 (0.12)	233 (81.5)
OMC-SXB-11 (US)	36/36 0/36 30 y (18-55)	4.5 g	Fasting state	142 (34.2)	0.75	0.57 (0.30)	289 (109)
			30min after high-fat breakfast	60.1 (20.1)	2.00	0.68 (0.22)	188 (80.0)

Summary of Pharmacokinetic parameters of GHB in Patients with Narcolepsy

Study (country)	Subjects entered/completed males/females	Treatment		Mean (SD) PK parameters (median if no SD shown)			
				Cmax (ug/ml)	Tmax (min or h)	T½ (min or h)	$AUC_{0\text{-}inf}$ (Ug.min/ml or ug.h/ml)
OMB-GHB-4 (US)	6/6 4/2 51 y (19-62)	2 x 3g (4h apart)	Dose 1	628 (27.4)	400 (6.2)	530 (19.3)	17732 (4867)

Study (country)	Subjects entered/completed males/females	Treatment		Mean (SD) PK parameters (median if no SD shown)			
				Cmax (ug/ml)	Tmax (min or h)	T½ (min or h)	$AUC_{0\text{-}inf}$ (Ug.min/ml or ug.h/ml)
			Dose 2	912 (25.6)	357 (7.0)		
OMC-SXB-10	13/13 3/10 39 y (23-52)	4.5g	Initial dose	900 (30.8)	0.75	0.67 (0.17)	226 (74 6)
			After 8 w	104 (31.3)	0.50	0.67 (0.21)	254 (78 5)

3.2.4 Dose proportionality and time dependencies

Study OMC-SXB-9 in healthy volunteers and studies OMC-SX-10 OMC-GHB-4 in patients respectively addressed the issue of dose dependency and steady-state.

The non-linearity found in study OMC-SXB-9 has not been fully explained. Since sodium oxybate undergoes extensive first-pass metabolism (oral absolute bioavailability is about 28%), the non-linearity can be due to saturation of either pre-systemic or systemic elimination. A slight increase in the half-life is observed (see table 4 below), but statistical significance cannot be tested due to confounding factors such as divided dose and food effect.

Studies OMC-SXB-10 and OMC-GHB-4 did not show evidence of a strong dose-dependency.

Overall, a careful monitoring upon individual dose titration is recommended and is reflected in the SPC.

Table 4: Dose proportionality study

	1st dose		2nd dose			
	Cmax (µg/mL)	Tmax (h)	Cmax (µg/mL)	Tmax (h)	AUC (µg.h/mL)	t1/2 (h)
4.5 g	26.6	0.85	60.1	0.64	138	0.59
9 g	77.6	1.17	142	0.72	518	0.83

3.2.5 Special populations

The applicant did not perform studies in special populations: sodium oxybate is not intended for children or elderly because narcolepsy/cataplexy has a very low prevalence in those age brackets.

As sodium oxybate is eliminated almost exclusively via biotransformation, no renal impairment effects are expected. Therefore the only recommendation in patients with compromised renal function is a possible reduction in sodium intake since 4.5 g of sodium oxybate contains 0.75 g of sodium. This is stated in the SPC.

Based on a published study, the dosing recommendation in the SPC for patients with hepatic impairment, is to halve the starting dose in such patients, and to monitor closely the response to dose increments.

3.2.6 Pharmacokinetic interaction studies

GHB is metabolised via beta-oxidation or tricarboxylic acid cycle (Krebs) pathways. Therefore no involvement of CYP isoenzymes is expected. This has been confirmed by *in vitro* studies for CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.

Four drug-drug interaction studies have been performed (OMC-SXB-12,-14,-17,-24). No significant interactions have been detected of either GHB on zolpidem, protriptyline and modafinil or of the same drugs on GHB. However, the rate of adverse events in co-administration with protriptyline, a tricyclic antidepressant, was increased both in healthy subjects and patients. Therefore a potential pharmacodynamic interaction cannot be excluded with antidepressants. This is stated in the SPC.

Omeprazole did not show significant interaction on GHB pharmacokinetics.

There is also a suggestion in primates that the antiepileptic drugs valproate, ethosuximide and phenytoin can influence activity of gamma-hydroxybutyrate dehydrogenase in the initial conversion of gammahydroxybutyrate to succinic semialdehyde (Snead 1978a, 1978b). As GHB is metabolised by gamma hydroxybutyrate (GHB) dehydrogenase, there is a potential interaction with drugs that inhibit this enzyme. These drugs include but are not limited to valproate, phenytoin, ethosuximide, salicylate, amobarbital, disulfiram and cyanide, and trimethadione. As the interaction of Xyrem with drugs that inhibit GHB dehydrogenase was not studied in human subjects, it is not known clinically what effects these drugs would have if administered concurrently (i.e. in patients being treated with anticonvulsants). L-DOPA, a precursor to dopamine, which increases dopamine levels, has also been shown to potentiate Xyrem's hypnotic effects, although studies in primates have shown that co-administration of L-DOPA and GHB may result in a reduction in serum concentrations of GHB.

3.3 Pharmacodynamics

3.3.1 Mechanism of action

The mechanism of action is largely unknown. The applicant did not produce any original data. The summary below is based in the published literature.

Sodium oxybate is an endogenous 4-carbon fatty acid that is thought to act as a neurotransmitter in the regulation of sleep cycles, blood flow, emotion, and memory. Its actions are thought to be mediated through brain receptors specific for GHB as well as through binding to GABA-B receptors. At low doses, the drug inhibits presynaptic dopamine release, while at high doses, dopamine release may be stimulated. It is believed that sodium oxybate decreases the symptoms of narcolepsy by inducing REM sleep and increasing delta sleep. The precise mechanism by which sodium oxybate produces anti-cataplectic activity in patients with narcolepsy is unknown.

3.3.2 Primary and Secondary pharmacology

Sodium oxybate is a central nervous system depressant, pharmacotherapeutic group: Other Nervous System Drugs, ATC code: N07XX04 hydroxybutyric acid.

Sodium oxybate is directed to the treatment of cataplexy in Narcolepsy and the model to propose this indication is based on the current understanding that narcolepsy symptoms should be categorised in 2 groups: 1) daytime sleepiness and sleep fragmentation; 2) Cataplexy and REM related symptoms.

Anesthetic induction is thought to occur from a general CNS depressant effect on the cerebrospinal axis, and occurs at higher dosages. Intoxication with sodium oxybate or GHB can produce severe symptoms including seizures, respiratory depression, CNS depression, coma, and death.

Endocrine effects
It is known from the literature that GHB exhibits effects on growth hormone, cortisol and prolactin.
Available literature data from human studies show that oxybate (gammahydroxybutyrate; GHB) consistently provokes small, short-lived increases in growth hormone (GH) release, whereas, the data from animal studies is less clear; vide infra. In contrast, evidence in the literature of any substantial effect of GHB on either Prolactin (PRL) or cortisol release is weak. Likewise, neither IGF-I nor IGFBP-3, indices of hypersecretion of GH (MacGillivray, 2001), are consistently altered (van Cauter, et al, 1997) and other hormones of the hypothalamic-pituitary axis appear to be unaffected by GHB, there being little or no effect on thyroid stimulating hormone, thyroxine, melatonin or luteinising hormone (Oyama et al, 1972, Gerra 1994a, van Cauter, et al, 1997).

Pharmacodynamic interactions

In the clinical trial database, more than 80 % of patients maintained concomitant stimulant use.

Stimulants such as methylphenidate, dextroamphetamine, methamphetamine, pemoline or modafinil are used commonly to treat the symptoms of daytime sleepiness in patients with narcolepsy. Tricyclic antidepressants (TCAs) - such as protryptiline, amitriptyline, chlomipramine, imipramine and trimipramine - or serotonin selective reuptake inhibitors (SSRIs) – such as fluoxetine, sertraline and paroxetine - are used to treat the REM-dissociation phenomena of cataplexy, hypnagogic hallucinations and sleep paralysis. The seven trials that comprise the clinical trial database did not include a trial designed to specifically investigate the potential pharmacodynamic interactions of sodium oxybate with other concomitant medications in this patient population. A re-analysis considering subgroups defined by the concomitant use of stimulants or tricyclic antidepressants was performed at the request of CHMP. No signals of a pharmacodynamic interaction were shown. However, due to the small numbers and the inherent limitation of post-hoc analysis a pharmacodynamic interactions with CNS stimulants or TCA antidepressants cannot be ruled out and this is reflected in the SPC.

3.4 Clinical efficacy

The use of sodium oxybate (sodium gamma hydroxybutyrate) in narcolepsy dates back to open-label clinical trials conducted by Broughton and Mamelak (1979 and 1980). These trials, along with subsequent open-label trials (Scharf et al, 1985; Mamelak et al, 1986; Montplaisir and Godbout, 1986), provided early evidence that sodium oxybate was effective in the treatment of narcolepsy symptoms.

Efficacy data from seven completed clinical trials, to support the use of sodium oxybate for the treatment of cataplexy associated with narcolepsy, are included in this application.

Controlled studies

There are four controlled studies:

• Randomized, double blind, placebo-controlled comparison of 3, 6 and 9 g of sodium oxybate (given in two divided doses) versus placebo in 136 patients treated for 4 weeks (OMC-GHB-2);

• Randomized, double-blind, placebo-controlled, crossover comparison of sodium oxybate (2 x 25 mg/kg) and placebo in 20 patients treated for 29 days (Scrima).

• Randomized, double-blind, placebo-controlled, crossover comparison of sodium oxybate (2 x 30 mg/kg) and placebo in 25 patients treated for 4 weeks (Lammers).

• Randomized, long-term, double-blind, placebo controlled study to compare continued sodium oxybate (3, 4.5, 6, 7.5 or 9 g/night in two divided doses) with placebo in 56 patients over a 2-week treatment period following long-term sodium oxybate treatment (OMC-SXB-21).

All studies included patients with an established diagnosis of narcolepsy, although the precise inclusion and exclusion criteria varied between studies. In all four studies, the number of cataplexy attacks is the primary efficacy variable (or is one of the stated primary efficacy variables) and was obtained from diary cards filled in by the patients. Pre-existing stimulant medication was maintained in all studies.

The two pivotal studies for determination of the effects against cataplexy are OMC-GHB- 2 and OMC-SXB-21.

All four controlled studies assessed various symptoms of narcolepsy, in addition to the change in number of cataplexy attacks, although the actual assessments varied between the studies. Several assessments were made by the patient (including the number of hypnagogic hallucinations, daytime naps, and daytime sleepiness). In the pivotal OMCGHB- 2 study, groups were compared for daytime sleepiness using the Epworth Sleepiness Scale and there was an investigator assessment of severity of the patient’s illness by the Clinical Global Impression of Change. The Scrima and Lammers studies

included polysomnogram recordings, but data were not available for the Lammers study report. Scrima published the polysomnogram and multiple sleep latency test data from his study (Scrima et al, 1990), but the results presented are based upon those presented in the Scrima study report. Patients in the Scrima study had a mean prevalence of cataplexy episodes of approximately 20 per week, whilst those in the Lammers study had approximately five episodes per week.

The results from the controlled studies demonstrating a reduction l in the number of cataplexy attacks and improvement of other narcolepsy symptoms are supported by those from three open label non-comparative studies:

Open-label studies

• The open label extension trial, OMC-GHB-3, extended the analysis of efficacy and safety from OMC-GHB-2 for an additional 12 months and served to further validate the endpoints in OMC-GHB-2. Patients began treatment at 6 g/night and the dose was subsequently adjusted to effect. The study included 117 treated patients.

• OMC-SXB-6 was an open-label 6-month study in 185 patients treated with 3, 4.5,

6, 7.5 or 9 g/day, titrated from a starting dose of 4.5 g/night to effect.

• OMC-SXB-20 was an open label study examining the effects of four doses of sodium oxybate (4.5 g, 6 g, 7.5 g and 9 g) on overnight polysomnogram recordings in 25 treated patients. In addition, patients from OMC-GHB-3, OMC-SXB-6 or the Scharf (safety) study could enter the long-term study OMC-SXB-7. An interim analysis, when 145/300 patients had been entered and treated, is included in this application.

In OMC-GHB-3, the number of cataplexy attacks is recorded, amongst other assessments. In the other open studies a narcolepsy symptom questionnaire was used to assess symptoms and response. The primary objective of study OMC-SXB-20 was not, however, to assess the effects against cataplexy but to characterise the polysomnographic sleep architecture in narcoleptic patients at the doses of sodium oxybate that were to be used therapeutically. In this study, patients were withdrawn from tricyclic antidepressant, specific serotonin-reuptake inhibitors and hypnotics over a 2-week period and were maintained for further 2-weeks without such medication. Overnight polysomnograms were recorded at the beginning and end of the 4-week period. Patients then received sodium oxybate at 4.5 g for 4 weeks, 6 g for 2 weeks, 7.5 g for 2 weeks and 9 g for 2 weeks and a polysomnogram was recorded on the last night of each dose level. The study assessments also included subjective determinations of the effects of sodium oxybate on daytime sleepiness (using the Epworth Sleepiness scale) and the well-established Maintenance of Wakefulness Test (MWT).

The pharmacokinetic studies have assessed a night time equally divided dose, between 4g and 9g. Because of the non-linear kinetics of sodium oxybate a decision was made not to further elevate the maximum dose of 9g, because of the potential for tolerability problems.

The minimum effective dose has also not been fully assessed. The clinical efficacy studies were designed to assess a lowest dose of 3g nightly in equally divided doses. This is based on the efficacy data that had been apparent in previous (non-sponsor, published literature) studies.

A decision was made to clinically evaluate dosing at night time, based on the rationale of mechanism of action, which propose that a normalisation of night time REM sleep will have effect on daytime REM phenomena (such as cataplexy) and also based on clinical experience in earlier trials.

3.4.1 Dose response studies

The studies designed by SCRIMA and LAMMERS were randomised, placebo controlled studies of investigator initiative that were performed several years before the pivotal trials. These 2 studies provide background data to the pivotal studies and can be considered therapeutic exploratory studies.

SCRIMA STUDY: The effects of gamma-hydroxybutyrate (GHB), 25 mg/kg orally at bedtime and 3 hours later, on cataplexy and sleep in narcolepsy patients: a doubleblind, placebo-controlled study (Scrima).

Objectives: To evaluate as primary variables average daily number of cataplexy attacks and objective daytime sleepiness using the sleepiness index determined by the multiple Sleep Latency Test (MSLT) in narcolepsy patients during treatment with GHB as compared with placebo (PLC) and baseline.

To evaluate as secondary variables average number of sleep attacks, average number of awakenings per night, dosing requirement of methylphenidate, feelings on awakening, mood in the morning and evening, sleep patterns identified on the polysomnogram (PSG), and average number of REM onsets determined by the MSLT during treatment with GHB as compared with placebo and baseline

Results:

The mean number of cataplexy attacks is summarized below; the data indicate that GHB was superior to placebo at Weeks 3 and 4 and overall. There was no evidence of carryover.

Treatment group	Mean (SE) number of cataplexy attacks per day						
	BL	Treatment phase				Overall	BL to end
		Week 1	Week 2	Week 3	Week 4		
GHB	2.9 (0.5)	1.4 (0.2)	1.4 (0.2)	0.9 (0.2)	0.9 (0.2)	1.2 (0.2)	2.9 to 1.2 (p = 0.007)
Placebo		1.5 (0.2)	2.0 (0.3)	2.1 (0.4)	1.9 (0.3)	1.9 (0.3)	2.9 to 1.9 (p = 0.117)
P value		NS	NS	0.005	0.004	0.013	

By week 4, GHB was superior to placebo for 16/19 patients (84 %). No cataplexy attacks were reported for 4/19 (21 %) of patients during week 4 of GHB compared with 1/19 (5 %) during week 4 of placebo.

Pre-study mean MSLT sleepiness index was 88.5. Although the mean sleepiness index was lower during GHB treatment than placebo treatment (87.2 versus 90.3) there was no significant treatment effect (p = 0.085).

The PSG results revealed statistically significant differences between GHB and placebo which are modest. With regard to overall sleep efficiency on Days 1 and 29 (84.4 % versus 88.1 %, p = 0.023), sleep latency (3.5 versus 2.5 min, p = 0.028), Stage 1 sleep (23.0 % versus 27.0 %, p = 0.042), Stage 3 sleep (5.5 % versus 2.8 %, p = 0.003), stage shifts (109.9 versus 129.2, p = 0.006), and number of objective awakenings (21.8 versus 26.9, p = 0.012). On Day 1, GHB and placebo differed significantly with regard to sleep efficiency (83.5% versus 87.8 %, p = 0.019), stage shifts (102.9 versus 125.1, p = 0.005), and number of objective awakenings (20.7 versus 25.1, p = 0.049). On Day 29, GHB and placebo differed with respect to stage 1 sleep (24.3 % versus 28.6 %, p = 0.026), Stage 3 sleep (6.7 % versus 2.3 %, p = 0.001), and number of objective awakenings (22.8 versus 28.6, p = 0.042).

There were no differences with respect to Stage 2 sleep, Stage 4 sleep, REM sleep or REM latency. There was also no difference in relationship to the number of MSLT REM onsets.

LAMMERS Study: Prospective, double-blind, cross-over, randomised study to assess the effect of gamma-hydroxybutyrate in patients with narcolepsy (Lammers)

Objectives: To investigate whether:

• gamma-hydroxybutyrate, in a double- blind study, has an effect on the REM -dissociation phenomena and possibly on the elevated inclination to sleep during the day;

• gamma-hydroxybutyrate affects the alertness during the day; and·

• gamma-hydroxybutyrate has a mood-improving effect.

Results: A Significant improvement was shown in the two primary efficacy parameters (global improvement and number of cataplexy attacks). In addition significant improvement was shown in daytime sleepiness, number of daytime sleep attacks and number of night-time awakenings. Its long-term safety was not determined in this trial, but the treatment was very well tolerated by the vast majority of the trial patients over a 4-week course of therapy.

3.4.2 Main studies

The two pivotal studies for determination of the effects against cataplexy are OMC-GHB-2 and OMC-SXB-21.

In OMC-GHB-2, patients were tapered from their existing anti-cataplexy treatment over a period of 1 day to 4 weeks and there was then a washout period of 5-28 days (dependent upon the half-life of the previous medication), followed by a baseline period of 2-3 weeks during which no cataplexy treatment was given. The double-blind comparative phase was followed by a 3-5 day period without any cataplexy treatment. Patients were randomized to a low (3 g), medium (6 g) or high (9 g) fixed dose of sodium oxybate, enabling comparison of each of the three doses against placebo.

STUDY OMC-GHB-2
Randomised, double-blind, placebo-controlled, parallel-group, multicentre trial comparing the effects of three doses of orally administered Xyrem (sodium gamma-hydroxy-butyrate or sodium oxybate or GHB) with placebo for the treatment of narcolepsy (OMC-GHB-2)

DESIGN:

Screening	**Washout**	**Baseline**	**Double-blind Treatment**	**Follow-up**
one day to 4 weeks	5-28 days	2 to 3 weeks	4 weeks	3-5 days
Visit 1	Visit 2	Visit 3	Visits 4 5 6	Visit 7
Withdrawal of treatment for cataplexy	No treatment for cataplexy		Placebo or GHB 3g, 6g, or 9g	No treatment for cataplexy

- **Study Participants**

Diagnostic criteria: Current diagnosis of narcolepsy for a least 6 months according to the following two items of criteria A as established by the American Sleep Disorders Association (ASDA): recurrent daytime naps or lapses into sleep than occur almost daily for at least 3 months; sudden bilateral loss of postural tone in association with intense emotion (cataplexy).

- **Treatments**

Sodium oxybate, 3 g, 6 g or 9 g, divided into two nightly doses

- **Objectives**

To evaluate and compare the efficacy of three doses (3 g, 6 g and 9 g) of sodium gamma-hydroxybutyrate and placebo in the treatment of the symptoms of narcolepsy.

To evaluate and compare the safety of GHB with placebo when used in a narcoleptic patient population.

- **Endpoints**

Primary efficacy parameter: total number of cataplexy attacks.
Secondary efficacy parameters:

- number of complete and partial cataplexy attacks,
- hypnagogic hallucinations,
- sleep paralysis episodes,
- excessive daytime sleepiness as measured by the Epworth Sleepiness Scale, number and duration of sleep attacks/inadvertent naps,
- number of night-time awakenings,
- total amount of sleep,

- severity of the patient's illness by Clinical Global Impressions of Change.

- **Sample size**

Planned: 104 patients (26 in each of four groups)

Studied: 136 patients (57 M, 79 F, mean 43.1 y); 34 (7 M, 27 F, mean 47.1 y) treated with 3 g/day, 33 (21 M, 12 F, mean 43.5 y) with 6 g/day, 35 (17 M, 18 F, mean 40.9 y) with 9 g/day and 34 (12 M, 22F, mean 40.8 y) with placebo.

- **Outcomes and estimation**

At 9 g, 4.5 g taken at bedtime and 4.5 g taken 2.5-4 hours later, sodium oxybate produced a significant improvement in total number of cataplexy attacks per week; the reduction was also significant for the 6 g dose in the FDA's reanalysis of results by ANOVA. The following table shows the results for both ANCOVA and ANOVA; the latter are shown after the /, where appropriate.

		Baseline	Endpoint	Change	P value v placebo
Placebo	N	33	33	33	
	Median	20.5	16.3	-4.3	
3 g	N	33	33	33	0.5235/0.5541
	Median	20.0	9.5	-7.0	
6 g	N	31	31	31	0.0529/0.0451
	Median	23.0	6.0	-9.9	
9 g	N	33	33	33/34	0.0008/0.0016
	Median	23.5	8.7	-16.1/-15.6	

The results are expressed as median and median percentage change from baseline below for Weeks 2 and 4/endpoint. The reduction seen at Week 2 in the placebo group did not change with further treatment, but further improvement was observed with 3 g and especially 9 g doses of sodium oxybate.

			Week 2		Week 4/endpoint	
		Baseline	Value	% change	Value	% change
Placebo	N	34	33	33	32	32
	Median	20.2	15.0	28.0	15.2	28.1
3 g	N	33	32	32	32	32
	Median	20.0	8.75	39.7	9.9	49.3
6 g	N	33	29	29	31	31
	Median	23.0	10.0	50.0	8.0	49.2
9 g	N	35	31	31	31	31
	Median	23.5	16.79	54.6	8.0	68.6

The percentage of subjects who became attack-free is relatively low (10 to 18%) but it is consistently higher in the sodium oxybate 9 g dose group, both by visit and overall. Results are shown in the following table:

Table 70.1: Number (%) of subjects who became attack-free, by dose of sodium oxybate: study OMC-GHB-2

	placebo			sodium oxybate								
				3 g/d			6 g/d			9 g/d		
Period	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
Visit 5 (during weeks 1 + 2 of DB treatment)	0	33	0	1	32	3.1%	1	29	3.4%	0	31	0%
Visit 6 (during weeks 3 + 4 of DB treatment	1	32	3.1%	0	32	0%	0	31	0%	5	31	16.1%
Visit 7 (during 3-5 day FU period)	2	31	6.5%	2	29	6.9%	1	29	3.4%	3	28	10.7%
Overall (from start of DB treatment to end of follow-up)	3	34	8.8%	2	33	6.1%	2	32	6.3%	6	34	17.6%

n= number of subjects who became attack free. N= total number of subjects with evaluable data.
Note: Includes only those subjects who had baseline data and data at a specified visit.
Source: Appendix 71-1:Table 7.1: GHB-02: Percentage of Patients Achieving 100% Reduction in Total Cataplexy Attacks, by Dose.

The clinical global impression is summarised below as responders (those who were much improved or very much improved) and non-responders (minimally improved, no change, minimally worse, much worse, very much worse).

The proportion of responders was notably and significantly higher in the 9 g group.

	Placebo	3 g	6 g	9 g
Responders	11 (32%)	14 (47%)	16 (52%)	24 (80%)
Non-responders	23 (68%)	16 (53%)	15 (48%)	6 (20%)
P value v placebo		0.3075	0.1368	0.0002

The median change in excessive daytime sleepiness as assessed by the Epworth Sleepiness Scale (ESS) is shown below.

		Baseline	Endpoint	Change	P value v placebo
Placebo (n = 33)	Median	19.0	17.0	-1.0	
3 g (n = 31)	Median	17.0	16.0	-1.0	0.1137
6 g (n = 30)	Median	17.0	13.5	-2.0	0.1860
9 g (n = 28)	Median	17.0	12.0	-3.5	0.0001

At baseline the number of patients with an ESS of 13 or higher in the placebo, 3 g, 6 g and 9 g groups was 30, 28, 27 and 25, respectively. At endpoint, 2, 7, 9 and 12 of these patients had scores of less than 13 and 1, 3, 3, and 6 had scores of less than 10 (= normal).

Other efficacy variables showed a positive effect of sodium oxybate. The median change from baseline in the number of inadvertent nap/sleep attacks in the placebo, 3 g, 6 g and 9 g groups from baseline to endpoint was -0.26, -0.20, -0.48 and -0.48 and the 6 g ($p = 0.0497$) and 9 g groups ($p = 0.0122$) differed significantly from the placebo group. The median change from baseline to endpoint in the number of awakenings per night was 0.20 for placebo, -0.25 for 3 g, -0.21 for 6 g and -0.91 for 9 g. The 9 g and placebo groups differed significantly ($p = 0.0035$).

There were no significant differences between groups with regard to the change from baseline to endpoint in median number of hypnagogic hallucinations, sleep paralysis episodes, total amount of sleep and duration of inadvertent naps/sleep attacks.

After treatment was stopped, the number of attacks of cataplexy increased: in the 9 g/day group, the median change in the number of attacks per week from end of treatment to follow-up 3-5 days later was +4.7 ($p = 0.0017$, $n = 27$) and in the 6 g/day group the median change was +6.1 ($p = 0.0001$, $n = 29$). The changes in the placebo and 3 g groups were not significant (+1.9, $n = 30$, and +2.3, $n = 29$). There was no evidence of rebound: the median change in the number of weekly cataplexy attacks from baseline to 3-5 days after end of treatment was -11.6 for the 9 g/day group ($p = 0.0001$). The number of attacks was thus still lower than at baseline (median 29.2).

3.4.3 STUDY OMC-SXB-21

Randomised, double-blind, placebo-controlled, multicentre trial to assess the long-term efficacy of orally administered Xyrem (sodium oxybate) when compared to placebo (OMC-SXB-21)

DESIGN

Table 1. OMC-SXB-21 Trial Design

Phase I Screening	Phase II Lead-In	Phase III Double-Blind Treatment
3 to 5 Days	14 ± 2 Days (Week 1, Week 2)	14 ± 2 Days (Week 1, Week 2)
Xyrem at established dosage	Single-blind Xyrem at established dosage	Xyrem at established dosage
		Placebo
Stimulant use permitted TCA/SSRI use not permitted		

Visit 1 (Randomization) — Visit 2 — Visit 3 — Visit 4

This is a relapse-prevention like design but in this case patients were already treated with GHB for several years. The test situation consisted in withdrawing patients from their usual treatment by switching to placebo under double-blind conditions. This study allows the evaluation of the risk of a withdrawal and rebound phenomenon.

- **Objectives**

To provide evidence for the long-term efficacy of Xyrem based on the return of cataplexy symptoms upon cessation of a minimum of 6 months of open label treatment with Xyrem and to evaluate the safety of Xyrem.

- **Outcomes/endpoints**

Efficacy: Change in the number of cataplexy attacks from the baseline (2- week single-blind lead-in phase) to endpoint (2-week double-blind treatment phase).
Safety: Assessment of AEs and changes in clinical laboratory results, vital signs, and physical examinations.

- **Results**

Table 4. Demographics and Baseline Characteristics by Treatment Group

Characteristics	Total (N=55)	Treatment Group: Xyrem (N=26)	Treatment Group: Placebo (N=29)	p-Value
Cataplexy attacks (2-week baseline)				
N	55	26	29	0.436
Mean	12.6	9.0	15.7	
SD	31.75	19.25	39.88	
Median	3.0	1.9	4.0	
Minimum	0.0	0.0	0.0	
Maximum	197.0	86.8	197.0	
Daily Dosage of Xyrem at Screening (n, %)				
3.0 g/d	2 (4%)	1 (4%)	1 (3%)	ND
4.5 g/d	9 (16%)	4 (15%)	5 (17%)	
6.0 g/d	15 (27%)	7 (27%)	8 (28%)	
7.5 g/d	15 (27%)	7 (27%)	8 (28%)	
9.0 g/d	14 (25%)	7 (27%)	7 (24%)	

ND = Not determined. SD = Standard deviation.

The baseline characteristics of the 2 groups differ in parameter that constitutes the primary endpoint – number of cataplexy attacks. At baseline, the number of cataplexy attacks were much higher in the placebo group (median =4.0) than in the active group (median=1.9). This is due to the wide inter-patient variability in the frequency of cataplexy attacks.

There was no change in the number of cataplexy attacks from baseline (2-week single-blind treatment ith Xyrem only) to endpoint (2-week double-blind treatment with Xyrem or placebo) in the Xyrem

group (median change 0.0), while cataplexy attacks increased by a median of 21.0 in the placebo group (see table). This difference was statistically significant ($p < 0.001$) when analysed by an ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction. The change from baseline in the number of cataplexy attacks by week during the double-blind period mirrors the overall change from baseline: no change in the Xyrem group (median change 0.0, each week), while cataplexy attacks increased in the placebo group by a median of 4.2 in Week 1, and 11.7 in Week 2.

The results (number of cataplexy attacks/week) are shown by week in the next table.

	Xyrem			Placebo		
	Lead-in	DB	Change	Lead-in (Xyrem)	DB	Change
Week 1						
Mean (SD)	4.5 (9.62)	5.3 (11.84)	0.8 (7.48)	7.9 (19.94)	21.1 (35.13)	13.2 (22.02)
Median	0.9	1.0	0.0	2.0	7.0	4.2
Min-max	0.0-43.4	0.0-50.8	-15.4-25.2	0.0-98.5	0.0-126.0	-7.5-87.5
Week 2						
Mean (SD)	4.5 (9.62)	7.2 (18.66)	2.7 (13.74)	7.9 (19.94)	29.7 (47.30)	21.8 (35.16)
Median	0.9	0.5	0.0	2.0	13.0	11.7
Min-max	0.0-43.4	0.0-87.5	-10.7-62.0	0.0-98.5	0.0-168.0	-7.5-143.5

Rebound reactions in term of efficacy were characterized as a return to a level of cataplexy attacks per week that exceeded the original (pre-treatment) baseline levels.
Relative to subjects who remained on sodium oxybate, in subjects in the placebo group there was a small increase in the number of cataplexy attacks during the first and the second week of interruption of treatment with sodium oxybate (Week 3 and Week 4 of the study). The median change from baseline in the number of cataplexy attacks/week was 4.2 during the first week after cessation of sodium oxybate, and 11.7 in the second week.
Thus there is evidence of a gradual increase in incidence of cataplexy on withdrawal of treatment. This is reflected in the SPC (section 4.4)
Withdrawal symptoms are discussed in the Clinical Safety section of this report.

Open-label supportive studies

Long-term, open-label, multi-centre extension trial of orally administered Xyrem (sodium gamma-hydroxybutyrate) for the treatment of narcolepsy symptoms.

OMC-GHB-3 (US) was a long-term, Phase III, open-label, multicentre extension trial with the primary objective of evaluating the safety, and the secondary objective of evaluating the efficacy of sodium oxybate when used for 12 months in patients with narcolepsy.

The dose, calculated as the average dose used by the patient over the course of their involvement in the first 12 months of the trial, was 3 g for 15 patients, 4.5 g for 20, 6 g for 37, 7.5 g for 25 and 9 g for 20 patients. The total number of patients included in the analysis of the number of cataplexy attacks was 103 at 1 month, and reduced to 75 at 12 months and 52 at 18 month. The greatest reduction in number of cataplexy attacks occurred during the first month of sodium oxybate treatment. The change was significant at every visit ($p < 0.001$). There was no difference between doses (patients being titrated to clinical effect). The improvement in the number of cataplexy attacks was paralleled by an improvement in excessive daytime sleepiness as assessed using the Epworth Sleepiness Scale (ESS). At 1 month, the median change in the number of cataplexy attacks per week was -15.08 (-76.7% reduction from baseline), and the median change in ESS was -3.50. At 6 and 12 months, the median reduction in number of cataplexy attacks was -19.00 (-92.5%) and - 23.0 (-93.1%), respectively. The corresponding change in ESS was -5.0 at each of these time-points.

Open-label, multicentre 6-month trial of Xyrem (sodium oxybate) oral solution for the treatment of narcolepsy in trial drug-naïve patients

The OMC-SXB-6 trial (US) was a Phase III, open-label, multicentre trial with the primary objective of evaluating the safety and the secondary objective of evaluating the efficacy of sodium oxybate when

titrated from a starting dosage of 4.5 g/d to optimal effect in patients with narcolepsy for up to 6 months. Total daily dosages were 3, 4.5, 6, 7.5, or 9 g/d.

A total of 185 patients entered and 140 patients completed the trial. Other than having a history of cataplexy (i.e., > 0), frequency of cataplexy was not specified by this protocol, and was not quantified at baseline. A categorical questionnaire administered at baseline (Visit 2), indicated that in the preceding week patients had experienced between 0 and 50 (or more) attacks per week.

At baseline the number of cataplexy attacks per week was none for 41 patients (23%), 1- 10 for 86 (48%), 11-25 for 35 (19%), 26-50 for 11 (6%) and more than 50 for 7 (4%).

The last dose of sodium oxybate received was 3 g for 4 patients, 4.5 g for 52 patients, 6 g for 73 patients, 7.5 g for 27 patients and 9 g for 29 patients. The 9 g group was predominantly male (others were predominantly female) and also had higher mean weight and height suggesting that male, heavier and/or taller patients may require higher dosage.

Long-term, open-label, extension trial of Xyrem (sodium oxybate) oral solution for the treatment of narcolepsy.

OMC-SXB-7 was a long-term open label extension trial; patients who had participated in OMC-GHB-3, OMC-SXB-6 or the Scharf (safety) study were eligible.

Efficacy has been summarised as the change from baseline to last observation on trial medication. The proportion of patients with no cataplexy attacks or with a significant decrease since the previous week was 77% overall and 100%, 100%, 70%, 69% and 87% for those taking 3 g, 4.5 g, 6 g, 7.5 g and 9 g, respectively. Improvement in daytime sleepiness had also occurred with 52% overall showing no sleepiness or an improvement; the proportion showing improvement on 3 g, 4.5 g, 6 g, 7.5 g and 9 g were 100%, 38%, 49%, 50% and 62%. The overall proportions with improvement in inadvertent naps/sleep attacks (day), awakenings at night, hypnagogic hallucinations, and sleep paralysis episodes were 57%, 55%, 90% and 92%. Overall, 92% of patients regarded themselves as much improved or somewhat improved in overall narcolepsy symptom assessment.

Open-label, multi-centre trial evaluating the effects of four doses of orally administered Xyrem (sodium oxybate) on overnight polysomnographic recordings

The primary objective of OMC-SXB-20 was to characterize the polysomnographic sleep architecture in narcoleptic patients at four escalating doses of sodium oxybate (4.5, 6, 7.5 and 9 g/day) over a 10-week exposure period. Daytime function was also assessed. Safety was assessed on the basis of adverse events, clinical laboratory results, ECG, vital signs and physical examinations

The following conclusions are derived from the objective and subjective measures of daytime sleepiness:

• The administration of sodium oxybate produced a significant increase in daytime sleep latency as measured by the MWT. This dose-dependant increase averaged 3.7 minutes ($p = 0.038$) after 4 weeks of 4.5 g nightly that further increased to a mean improvement of 6.1 minutes ($p < 0.001$) following the nightly 9.0 g dose.

This measured response is additive to that produced by concomitant stimulant dosing.

• The presence of sleep-onset REM periods (SOREMPs) during MWT, which occurred in 18 of 21 patients (86%) at baseline, decreased to 13 of 21 (62%) following 4 weeks of 4.5 g sodium oxybate nightly. SOREMPs further decreased to 6 of 20 patients (30%) following the 9.0 g dose.

• The ESS total score significantly decreased in a dose-dependant manner by the nightly administration of sodium oxybate. The median total score of 20 at baseline improved by 2 points following the 4.5 g dose regimen ($p<0.001$), increasing across the dose range up to 7 points after the 9.0 g dose ($p<0.001$).

The patients in the current trial reported substantial improvements in subjectively determined daytime narcolepsy symptoms including the incidence of cataplexy attacks, the number of inadvertent naps as well as decreased daytime sleepiness, and increased the ability to concentrate and a perception of overall improvement in their narcolepsy while taking nightly doses of sodium oxybate.

3.4.4 Discussion on clinical efficacy

Cataplexy is one of the hallmarks of narcolepsy although it is possible to have narcolepsy without the presence of cataplexy, either because it did not manifest yet or because the clinical situation is a variant of the classical narcolepsy. At a given moment 60 to 70% of the patients have cataplexy attacks. Out of these only a fraction has cataplexy attacks that because of their frequency or severity need treatment. These patients are about 30% of all narcoleptic patients.

Narcolepsy symptoms are categorised in 2 families those that are REM related, meaning that they result for the intrusion of REM phenomena in a disrupted sleep/wakefulness cycle. The REM phenomena are cataplexy, hypnagogic hallucinations and sleep paralysis. The other family of symptoms are related with excessive daytime sleepiness. Nevertheless these 2 families are not completely independent and it is likely that improvement in one of them will reflect in a benefit in the other. However it is possible to produce an independent effect which is the case of modafinil that have a beneficial effect in daytime sleepiness without affecting cataplexy. Thus, efficacy must be demonstrated either for cataplexy or daytime sleepiness or for both.

In the case of GHB the applicant aimed to demonstrate the efficacy of GHB on cataplexy, although daytime sleepiness was also evaluated.

No dose-finding studies were conducted but the pivotal trial tested 3 doses (3, 6 and 9g/day).

There are 2 phase II trials (placebo controlled, crossover) which were of investigators initiative. One was GCP compliant the other not. In addition, there was a pivotal parallel, placebo-controlled trial. In these trials the duration of the double-blind treatment was not longer than 4 weeks. In the pivotal trial and one of the phase II trials patients had about 20 cataplexy attacks/week at baseline, in the other phase II trial patient were much less affected - 5 attacks/week. All patients were older than 16, and most of them older than 18 years old. In these conditions GHB reduced consistently the number of cataplexy attacks. This reduction was translated in a global improvement only in the high dosage of the pivotal trial. The open-label trials and extension of trials that are present in the dossier are also supportive of an effect in the number of cataplexy attacks. They also suggest that the positive effect of GHB is built up during time which makes 4 weeks a short time frame to assess the overall effect.

In conclusion GHB is efficacious in reducing cataplexy attacks. The 9g dose is clearly the most efficacious dose (the only dose that produces also a consistent effect in other symptoms) but this extra efficacy is at cost of more side-effects. The current recommended posology is starting at 4.5 g/day and going upwards according to efficacy and tolerability although such a regimen has not been studied in a randomised controlled trial. The effect on cataplexy seems to be maintained during several years but the proof of this is not very robust because it is based on the open-label trials and in the relapse prevention trial. This suggests that in fact, the effect is maintained, but is confounded by an imbalance of severity at baseline between placebo and active group and by putative withdrawal effects.

The data available is consistent with the existence of a mild withdrawal syndrome and rebound cataplexy upon suspension of treatment. This is reflected in the SPC

In addition to the effect in cataplexy, GHB seems to have a positive effect on daytime sleepiness when the higher doses are used (9 g in the OMC-GHB-2 trial) and in the long-term (open label extensions). Usually the effect on daytime sleepiness is paired with less inadvertent naps/sleep attacks and less awakenings during the night which are probably related to the increase in slow wave sleep seen in the polysomnograms. The data that supports an effect on daytime sleepiness is not as strong than the one on cataplexy. Therefore the effect on daytime sleepiness is not considered to be demonstrated.

The populations studied do not include patients below 16 years of age, and the strata between 16 and 18 years old is very small. Although the disease starts at adolescence, mainly with excessive daytime sleepiness, the cataplexy attacks, affecting a fraction of the patients, occur on average 6 year from the onset of the other symptoms. Therefore, the indication has been limited to adults and this is reflected in the SPC.

3.5 Clinical safety

Safety data were collected in all clinical studies included in this application.

Analyses of adverse events in phase I (clinical pharmacology) studies, one additional study (OMC-SXB-24) is included, but one study OMC-GHB-4 is excluded. The latter study included only six patients who were part of the main Scharf study and none of them experienced any adverse events.
The Scharf study is a long-term, open-label, retrospective compilation of safety data from 143 narcoleptic patients treated with sodium oxybate for up to nearly 16 years under an investigator-held IND. The majority of the patients were treated at doses in the range established by previous investigators (3 g to 9 g) with most patients experiencing optimal benefit at doses of approximately 6 g (Scharf et al, 1985).

There is also a retrospective study- the Scharf study- that only contributes with safety data and which was not described in the efficacy section.

3.5.1 Patient exposure

In total, 421 patients were treated with sodium oxybate for mean/median 219.7/174 days.

In total, 81 patients received placebo. Of those, three patients received placebo only, as the others in the placebo-controlled trial (Scrima) crossed over to sodium oxybate treatment (or vice versa), or entered studies in which they received sodium oxybate after receiving placebo in OMC-GHB-2. All placebo-treated patients in OMC-SXB-21 had previously received sodium oxybate treatment.

The number of patients for whom data from clinical efficacy and safety studies have been analysed in MedDRA, is shown in the following table.

Source of Adverse Event Data for Clinical Efficacy and Safety Studies

	Study	**Number (%) of patients**
Study	SCRIMA	20 (5%)
	OMC-GHB-2	136 (32%)
	OMC-GHB-3	118 (28%)
	OMC-SXB-6	185 (44%)
	OMC-SXB-7	145 (34%)
	OMC-SXB-20	22 (5%)
	OMC-SXB-21	56 (13%)

The majority of subjects were prescribed sodium oxybate at doses below 9 g/d. In study OMC-SXB-6, over two-thirds of subjects received 4.5 or 6 g/d as the last dose; in the Scharf study, over three-quarters of subjects took the 4.5 or 6 g/d dose for the longest duration; in study OMC-GHB-3, just under 50% of subjects received an average dose of 4.5 or 6 g/d. This is summurised in the following table:

Table 44a.3: Number (%) of subjects, by dose of sodium oxybate prescribed in study OMC-SXB-6, study OMC-GHB-3 and the Scharf study

	sodium oxybate (g/d)					
Study		**3.0**	**4.5**	**6.0**	**7.5**	**9.0**
	N	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
OMC-SXB-6 (last dose) [1]	185	4 (2.2%)	52 (28.1%)	73 (39.5%)	27 (14.6%)	29 (15.7%)
Scharf study (dose taken for the longest duration)	143	5 (3.5%)	49 (34.3%)	62 (43.4%)	18 (12.6%)	9 (6.3%)
OMC-GHB-3 (average dose) [2]	117	15 (12.8%)	20 (17.1%)	37 (31.6%)	25 (21.4%)	20 (17.1%)

Note 1: in study OMC-SXB-6, of the 4 subjects on 3 g sodium oxybate (last dose), 3 had their dose decreased (from 4.5 g) for AEs, but did not report improvement of their cataplexy attacks at the 3 g dose. One subject had two reports of no attacks in the past week and one report of a significant increase on the 3 g dose. This subject had had his dose of SSRI decreased.

Note 2: in study OMC-GHB-3, it is not possible to interpret the effects of a 3 g sodium oxybate dose because the dose was frequently modified and the reason for changes in dose were not recorded systematically

Source: adapted from Appendix 44a-4: Table 7, page 74, CSR OMC-SXB-6; Appendix 44a-5: Table 1, page 45, CSR Scharf study; Appendix 44a-6: Table 6, page 87, CSR OMC-GHB-3.

3.5.2 Adverse events

Table 7: Incidence of More Common Adverse Events by Dose of Sodium Oxybate at Onset

SOC	Event (preferred term)	All					Treatment-related				
		3	4.5	6	7.5	9	3	4.5	6	7.5	9
Number assessed		94	288	312	138	140	94	288	312	138	140
Gastrointestinal disorders	Abdominal pain upper	2 2%	6 2%	7 2%	2 1%	5 4%	1 1%	4 1%	3 1%	0	3 2%
	Diarrhoea	2 2%	4 1%	13 4%	4 3%	7 5%	1 1%	2 1%	4 1%	0	2 1%
	Nausea	9 10%	22 8%	36 12%	11 8%	31 22%	7 7%	18 6%	29 9%	9 7%	25 18%
	Vomiting	1 1%	6 2%	14 4%	2 1%	11 8%	1 1%	3 1%	10 3%	2 1%	7 5%
	SOC any	19 20%	46 16%	67 21%	17 12%	43 31%	11 12%	30 10%	40 13%	10 7%	32 23%
General disorders & admin. site conditions	Fatigue	5 5%	4 1%	11 4%	2 1%	2 1%	4 4%	2 1%	7 2%	0	1 1%
	SOC any	17 18%	26 9%	44 14%	12 9%	24 17%	10 11%	16 6%	20 6%	4 3%	14 10%
Metabolism & nutrition disorders	Anorexia	1 1%	0	0	0	6 4%	1 1%	0	0	0	6 4%
	SOC any	5 5%	6 2%	7 2%	3 2%	10 7%	2 2%	3 1%	3 1%	0	7 5%
Nervous system disorders	Dizziness	16 17%	12 4%	32 10%	9 7%	23 16%	10 11%	8 3%	26 8%	6 4%	21 15%
	Headache	17 18%	39 14%	35 11%	9 7%	22 16%	10 11%	18 6%	16 5%	3 2%	9 6%
	SOC any	33 35%	67 23%	89 29%	22 16%	52 37%	21 22%	42 15%	55 18%	14 10%	42 30%
	Abnormal dreams	0	3 1%	2 1%	3 2%	2 1%	0	3 1%	2 1%	1 1%	2 1%
Psychiatric disorders	Confusional state	3 3%	3 1%	8 3%	3 2%	4 3%	2 2%	3 1%	7 2%	3 2%	4 3%
	Nightmare	3 3%	6 2%	6 2%	2 1%	0	1 1%	6 2%	4 1%	1 1%	0
	Sleep walking	1 1%	7 2%	10 3%	6 4%	6 4%	1 1%	7 2%	10 3%	6 4%	6 4%
	SOC any	17 18%	37 13%	60 19%	19 14%	32 23%	8 9%	29 10%	40 13%	15 11%	29 21%
Renal & urinary disorders	Enuresis	2 2%	7 2%	8 3%	6 4%	11 8%	2 2%	5 2%	7 2%	6 4%	10 7%
	SOC any	3 3%	10 3%	17 5%	7 5%	17 12%	3 3%	7 2%	9 3%	7 5%	13 9%
Source; Table 2.7.4.2.1 and 2.7.4.3.1 and Tables 6 and 21 (Clinical) in Module 5.3.5.3.2 (Studies OMC-GHB-2, OMC-GHB-3, OMC-SXB-6, OMC-SXB-7, OMC-SXB-20, OMC-SXB-21 and the Scrima study)											

The results (shown for all events combined, irrespective of relationship to treatment) were, in general, good agreement with those from all integrated studies. The most common events in sodium oxybate-treated patients that were observed in a higher proportion of sodium oxybate-treated patients, when compared to placebo, were nausea, vomiting, dizziness, headache and enuresis. However, many more events were recorded for a low percentage of sodium oxybate-treated patients and for none or just one placebo treated patient. These included sleep paralysis, abnormal dreams, nightmares and sleep disorder. Blurred vision is also listed as a common side effect for which a possible pharmacodynamic is not proven.

3.5.3 Serious adverse event/deaths/other significant events

The only studies in which there were any deaths were the long-term Scharf study and study OMC-SXB-7 (a long-term, open extension of OMC-GHB-3, OMC-SXB-6 and the Scharf study). Eleven deaths (7.7 %) were reported in the Scharf study. None of the deaths was considered related to sodium oxybate.

Two deaths have been reported in study OMC-SXB-7, both of which were suicides. One suicide (patient 0531, coded as death) was due to multiple drug toxicity that included toxic levels of six psychotropic drugs other than sodium oxybate. The second suicide (patient 0936) was a patient with a

history of depression and a subsequent suggested diagnosis of bipolar disease. This event was officially ruled as a death due to cardiovascular disease (without autopsy by the Medical Examiner) but later evidence pointed to a possible overdose that included lithium, Paxil, and Percocet as well as sodium oxybate.

3.5.4 Laboratory findings

None of the laboratory changes raises a concern.

3.5.5 Safety in special populations and drug abuse

GHB is a known drug of misuse producing purported euphoric and/or hallucinogenic states.

The clinical trials and post-marketing data for Sodium oxybate have not revealed any clear evidence of abuse in patients.

It should also be noted that 2,021 patients have registered for Xyrem use since US approval in July 2002, and there have been no premature refill requests or reports of theft or loss. However in Europe a risk management system as strictly controlled as in the US will not be possible.

3.5.6 Withdrawal and rebound

Literature reports (Friedman et al, 1996, Galloway et al, 1997) indicate that abrupt discontinuation of high-dose chronic sodium oxybate results in withdrawal symptoms including insomnia, anxiety, and tremors. Of these, insomnia, which generally resolved within 3 days, was the most consistently described symptom, even in less heavy sodium oxybate users. Hallucinations have also been reported (Hernandez et al, 1998).

In study OMC-SXB-21, the incidences of subjects reported to have AEs, related AEs or severe AEs were higher in the group switched to placebo when compared to the group that continued with sodium oxybate therapy in the final 2-week double-blind treatment period, but these differences were small.
Five of the individual AEs might represent possible symptoms of sodium oxybate withdrawal. These were reported only in subjects in the placebo group: anxiety (n=2; 7%), dizziness (n=1; 3%), insomnia (n=1; 3%), sleep disorder (n=1; 3%) and somnolence (n=1; 3%).
Although these symptoms might have represented possible symptoms of mild sodium oxybate withdrawal, they may also be consistent with the recurrence of symptoms of narcolepsy.
In study OMC-GHB-2, during the 3-5 day follow-up period following discontinuation of sodium oxybate, in each dose group (sodium oxybate 3 g/d, 6 g/d, 9 g/d and placebo), with the exception of headache (n=2 in the groups who had received sodium oxybate 6 g/d or 9 g/d) and pain (n=2 in the group who had received sodium oxybate 9 g/d), only one subject was reported to have each of the individual AEs.
Overall, although the data do not show clear evidence of a withdrawal syndrome, a mild withdrawal syndrome cannot be excluded. This is reflected in the SPC (section 4.4. and 4.8)
Rebound reactions have been addressed in the clinical efficacy section of this report.

3.5.7 Safety related to drug-drug interactions and other interactions

There are no analyses of safety by concomitant treatments. Potential drug interactions with zolpidem, protriptyline, modafinil and omeprazole were analysed in Phase I studies (OMC-SXB-12, OMC-SXB-14, OMC-SXB-17 and OMC-SXB-24, respectively).

3.5.8 Discontinuation due to adverse events

Thirty-five sodium oxybate-treated patients and one placebo-treated patient in the integrated clinical studies were withdrawn due to adverse events.

3.5.9 Post marketing experience

The commonly reported adverse events are consistent with those identified in clinical studies. No new safety issues have been identified when analysing the post marketing safety data for Xyrem.

3.5.10 Discussion on clinical safety

A major concern regarding the safety profile of sodium oxybate is the narrow safety margin between the efficacious dose and the toxic doses. The frequency of AEs increases with dose and this is clear at the dose of 9g/day. This dose level is very close to the toxic doses taking as shown by 3 cases that suffered either from impaired consciousness or respiratory depression at doses that were 2x or 3X the recommended dose given as a single administration.
Unfortunately, the clinical studies did not attempt to characterize dosing on a per/kg body weight basis. Therefore, the recommended method of administration is to initiate treatment with a starting dose of 4.5 g/d, divided in two, and going up according to efficacy and tolerability. In addition prescribers should be warned that in patients with concomitant sleep apnoea the benefit-risk of going above 6 g/d should be stringently evaluated.
Most common AEs are expected (vomiting, nausea, dizziness, sleep disorders).Regarding the occurrence of enuresis/incontinence, the mechanism is unknown, but as the phenomena is similar to "enuresis nocturna" the release of inhibitory mechanism is a putative mechanism.
An evaluation of the most likely hormonal changes by means of a specific study is planned as a follow-up measure.
The risk for withdrawal reactions is mild and will be further studied in a post marketing Pharmacovigilance study.
The abuse/misuse potential will be also closely monitored in a risk management strategy. In addition to the limitations inherent to the legal status of GHB (schedule IV of the UN convention of 1971), the illicit use will be mitigated by means of education materials to health professionals and patients, strict control of distribution and non-interventional post-marketing surveillance

4 Overall conclusions, benefit/risk assessment and recommendation

4.1 Quality

The simple synthesis and manufacture of the product are described and controlled in a relevant manner, and the specifications of the active substance and medicinal product are considered to be relevant for a product of this type. The stability of the product has been well-investigated, both in the unopened form, and with the adaptor and dosing system in place during use.

Satisfactory uniformity of dose has been demonstrated, and there are no unresolved quality issues that could have an impact on the benefit/risk balance for the patient.

4.2 Non-clinical pharmacology and toxicology

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. The cause of human narcolepsy and cataplexy is, as yet, unknown. Recent evidence points to the loss of hypocretin-containing neurons, possibly due to autoimmune attack, as a likely cause.

In addition to its sedative properties, GHB is a potent CNS depressant and may increase growth hormone secretion. The potential for acute respiratory depression after reintroduction of treatment in patients who might have developed tolerance is mentioned in the SPC (4.2) as well as a warning in case of concomitant administration with other CNS depressant, and especially alcohol. (SPC, 4.4 and 4.5)

The interactions resulting from the stimulation or inhibition of GHB dehydrogenase, namely with anticonvulsivant drugs and L-dopa are considered to be potentially relevant in the clinic and are mentioned in the SPC.(section 4.5 and 5.3).

The bioavailability in rats is about 50-80% and the clearance is rapid (T½ ≈1h) with extensive biotransformation which is not P450 dependant. The kinetic is non-linear, due to saturable mechanisms of both absorption and elimination resulting in reduced Cmax and increased AUC from linearity with increasing doses. As GHB is metabolised by γ hydroxybutyrate (GHB) dehydrogenase, there is a potential interaction with drugs that inhibit this enzyme. This is reflected in the SPC (sections 4.5 and 5.3)

In repeat-dose toxicity, treatment-related clinical signs were mainly related to sedation. Safety margins, based on body weight changes and salivary gland atrophy, are low or non-existent, which is is in accordance with the frequent occurrence in humans of adverse effects such as nausea, anorexia and parasympathetic disorders (blurred vision, enuresis and sweating).

GHB is nongenotoxic and not considered to present a carcinogenic risk to humans.

In reproductive toxicity studies, foetoxicity was observed in rats and rabbits. The use of GHB is not recommended during pregnancy or breast-feeding and this is reflected in the SPC.

Tolerance to GHB as well as cross-tolerance to alcohol have been clearly demonstrated in rodents. The potential of GHB to induce withdrawal phenomena, demonstrated in animal models, is low, and the relevance for humans will be monitored in the future during the post-authorisation phase.

4.3 Efficacy

The clinical programme aimed to demonstrate the efficacy of GHB on cataplexy although daytime sleepiness was also evaluated.

No dose-finding studies were conducted but the pivotal trial tested 3 doses (3, 6 and 9g/day).

There are 2 phase II trials (placebo controlled, crossover) which were of investigators initiative. One was GCP compliant the other not. In addition, there was a pivotal parallel, placebo-controlled trial. In these trials the duration of the double-blind treatment was not longer than 4 weeks. In the pivotal trial and one of the phase II trials patients had about 20 cataplexy attacks/week at baseline, in the other phase II trial patient were much less affected - 5 attacks/week. All patients were older than 16, and most of them older than 18 years old. In these conditions GHB reduced consistently the number of cataplexy attacks. This reduction was translated in a global improvement only in the high dosage of the pivotal trial. The open-label trials and extension of trials that are present in the dossier are also supportive of an effect in the number of cataplexy attacks. They also suggest that the positive effect of GHB is built up during time which makes 4 weeks a short time frame to assess the overall effect.

In conclusion GHB is efficacious in reducing cataplexy attacks. The 9g dose is clearly the most efficacious dose (the only dose that produces also a consistent effect in other symptoms) but this extra efficacy is at cost of more side-effects. The current recommended posology is starting at 4.5 g/day divided in two intakes and going upwards according to efficacy and tolerability although such a regimen has not been studied in a randomised controlled trial. The effect on cataplexy seems to be maintained during several years but the proof of this is not very robust because it is based on the open-label trials and in the relapse prevention trial. This suggests that in fact, the effect is maintained, but is confounded by an imbalance of severity at baseline between placebo and active group and by putative withdrawal effects.

The data available is consistent with the existence of a mild withdrawal syndrome and rebound cataplexy upon suspension of treatment. This is reflected in the SPC

In addition to the effect in cataplexy, GHB seems to have a positive effect on daytime sleepiness when the higher doses are used (9 g in the OMC-GHB-2 trial) and in the long-term (open label extensions). Usually the effect on daytime sleepiness is paired with less inadvertent naps/sleep attacks and less awakenings during the night which are probably related to the increase in slow wave sleep seen in the polysomnograms. The data that supports an effect on daytime sleepiness is not as strong as the one on cataplexy. Therefore the effect on daytime sleepiness is not considered to be demonstrated.

The populations studied do not include patients below 16 years of age, and the strata between 16 and 18 years old is very small. Although the disease starts at adolescence, mainly with excessive daytime sleepiness, the cataplexy attacks, affecting a fraction of the patients, occur on average 6 year from the onset of the other symptoms. Therefore, the indication has been limited to adults and this is reflected in the SPC.

4.4 Safety

A major concern regarding the safety profile of sodium oxybate is the narrow safety margin between the efficacious dose and the toxic doses. The frequency of AEs increases with dose and this is clear at the dose of 9g/day. This dose level is very close to the toxic doses taking as shown by 3 cases that

suffered either from impaired consciousness or respiratory depression at doses that were 2x or 3X the recommended dose given as a single administration.
Unfortunately, the clinical studies did not attempt the characterize dosing on a per/kg body weight basis. Therefore, the recommended method of administration is to initiate treatment with a starting dose of 4.5 g/d, divided in two, and going up according to efficacy and tolerability. In addition prescribers are warned that in patients with concomitant sleep apnoea the benefit-risk of going above 6 g/d should be stringently evaluated.
Most common AEs are expected (vomiting, nausea, dizziness, sleep disorders). Regarding the occurrence of enuresis/incontinence, the mechanism is unknown, but as the phenomenon is similar to "enuresis nocturna" the release of inhibitory mechanism is an hypothesis.
An evaluation of the most likely hormonal changes by means of a specific study is planned as a follow-up measure.
The risk for withdrawal reactions is mild and will be further studied in a post marketing Pharmacovigilance study. The objectives of the study are to obtain data about patients' compliance to instructions for using Xyrem, to monitor the adverse drug reactions (ADRs) and estimate their frequency, to obtain data on the potential of dependence, withdrawal syndrome, overdose, of Xyrem and to broaden the knowledge about adverse drug reactions in special populations; elderly, young.
The abuse/misuse potential will be also closely monitored in this post-marketing study as part of a risk management strategy. The illicit use will be mitigated by means of education materials to health professionals and patients, strict control of distribution and non-interventional post-marketing surveillance.

5 Benefit/risk assessment

The efficacy of sodium oxybate for reducing the number of cataplexy attacks in narcolepsy patients has been demonstrated.

The tolerability profile is good, but the potential toxic dose is close to the highest therapeutic dose of 9g/day and makes the adherence to a strict up-titration extremely important. Therefore the prescription is restricted to physicians with experience in sleep disorders.

Due to the well known potential of abuse of sodium oxybate, Xyrem is under special prescription.

Warnings and recommendations in order to use Xyrem are explained in the SPC, especially the dosing regimen (daily dose divided in two and not in fasting conditions), and several warnings in particular the risk of respiratory depression.

In addition, a post-marketing pharmacovigilance plan has been agreed in order to monitor closely the safety regarding the possible occurrence of respiratory depression, as well as the potential for rebound and withdrawal reactions. This Pharmacovigilance plan includes also a risk management programme in order to minimise the risks of misuse/abuse.

Overall, the benefit risk assessment of sodium oxybate is considered to be favourable.

6 Recommendation

"Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit/risk ratio of Xyrem in the "treatment of cataplexy in adult patients with narcolepsy" was favourable and therefore recommended the granting of the marketing authorisation as a special and restricted prescription.