TGA Pre-Submission Meeting to discuss applications for orphan designation and registration for Xyrem in the treatment of narcolepsy.

Briefing Document

UCB

February 2018

Contents

Please note that the references quoted in this document are not provided, however they are available upon request and would be included in the orphan drug designation submission.

UCB Pharma (Australia) Pty Ltd (UCB) is the Australian Sponsor for sodium oxybate (Xyrem) which is currently being supplied under Category B of the special access scheme (SAS) to patients with narcolepsy. Although Xyrem is not a core product, since 2015 there has been an ongoing demand from specialist sleep physicians, patients and carers for this medicine.

UCB wish to discuss with TGA at a pre-submission meeting the best means to register the product based on the available EU dossier and orphan designation.

1. Summary

Background information on the disease to be treated

Narcolepsy is a chronic neurological disorder of unknown aetiology that affects the normal sleep/waking rhythm. The First International Symposium on Narcolepsy (July 1975, France) (Guilleminault et al. 1976) produced the first consensus definition of narcolepsy: "A syndrome of unknown origin that is characterized by abnormal sleep tendencies, including excessive daytime sleepiness (EDS) and often disturbed nocturnal sleep, and pathological manifestations of Rapid Eye Movement (REM) sleep. The REM sleep abnormalities include sleep-onset REM (SOREM) periods and the dissociated REM sleep inhibitory processes, cataplexy and sleep paralysis. EDS and cataplexy and, less often, sleep paralysis and hypnogogic hallucinations are the major symptoms of the disease."

In this definition, narcolepsy is not simply excessive sleep, but rather an inability to maintain either wakefulness or consolidated sleep. Patients are typically prone to excessive sleepiness and unwanted episodes of sleep (inadvertent naps) during the daytime and disturbed sleep at night (fragmented night-time sleep). Shortly after the discovery of REM sleep (Aserinsky and Kleitman 1953), it was found that narcoleptic patients often enter REM sleep directly at night, suggesting that narcolepsy might involve abnormal REM sleep (Vogel 1960). In the same year, Rechtschaffen et al (1963) and Takahashi and Jimbo (1963) independently confirmed that the night sleep of narcoleptic patients often began with REM sleep and suggested that cataplexy, sleep paralysis and hypnogogic hallucinations were abnormal manifestations of dissociated REM sleep. This led to the generally accepted model that sleep disturbances seen in narcolepsy are divided into two distinct categories of disturbance: the sleep/wake distribution (EDS/inadvertent naps and fragmented night-time sleep) and abnormal REM sleep-related symptoms (cataplexy, hypnogogic hallucinations and sleep paralysis).

According to the American Academy of Sleep Medicine, second edition of the International Classification of Sleep Disorders (ICSD-2, 2005) there are two forms of narcolepsy, narcolepsy with cataplexy and narcolepsy without cataplexy. According to these definitions:

- The patient has a complaint of EDS occurring almost daily for at least 3 months.
- The diagnosis should be confirmed by nocturnal polysomnography (PSG) followed by a multiple sleep latency test (MSLT); the mean sleep latency on the MSLT is less than or equal to 8 minutes and two or more SOREM periods are observed following sufficient nocturnal sleep (minimum 6 hours) during the night prior to the test, for both narcolepsy with and without cataplexy; alternatively, for patients with narcolepsy with cataplexy,

hypocretin-1 levels in the cerebrospinal fluid (CSF) are less than or equal to 110 pg/ml, or one third of mean normal control values.
- The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder.
- Patients with narcolepsy with cataplexy should additionally have a definite history of cataplexy, defined as sudden and transient episodes of loss of muscle tone triggered by emotions.
- For a diagnosis of narcolepsy without cataplexy, typical cataplexy must not be present, although doubtful or atypical cataplexy-like episodes may be reported.

Research provides compelling evidence that most cases of narcolepsy with cataplexy are associated with the loss of hypothalamic neurons containing the neuropeptide hypocretin. Hypocretin is a neurotransmitter that appears to have important roles in sleep-wake regulation, neuroendocrine stasis, autonomic regulation and control of feeding behaviour (De Lecea et al. 1998, Sakurai et al. 1998). The cell bodies of hypocretin containing neurones are located in the postero-lateral hypothalamus and have widespread projections within the CNS (Peyron et al. 1998). Two active peptides - hypocretin-1 and hypocretin-2 - have been identified. With regard to sleep, the dominant activities of the hypocretin system appear to be maintenance of the waking state and suppression of entry into REM sleep (Sutcliffe and De Lecea 2002). Animal models show alterations of hypocretin neurotransmission in narcolepsy (Lin et al. 1998; Chemelli et al. 1998), while analysis of CSF from humans with narcolepsy with cataplexy has demonstrated the concentration of hypocretin-1 to be very low (Nishino et al. 2000). Post-mortem examinations of brains from narcoleptic patients have shown a dramatic decrease in hypocretin-containing cells (85-95%) and greatly diminished hypocretin messenger ribonucleic acid (mRNA) (Peyron et al. 2000; Thannickal et al. 2000). Genetic factors are also involved (first-degree relatives of narcolepsy patients have a higher risk of developing narcolepsy) and the higher incidence of the human leukocyte antigen (HLA) DQB1 *0602 subtype in narcoleptic individuals compared with the general population suggests a possible autoimmune effect. On the basis of the HLA association, loss of hypocretin neurons and age of disease onset, it has been hypothesized that narcolepsy results from an autoimmune effect in genetically susceptible individuals. However, no autoimmune triggers or antibodies have yet been identified (Mignot et al 1995).

In a minority of cases of narcolepsy without cataplexy, the disease is associated with the loss of hypothalamic neurons containing the neuropeptide hypocretin, as described for narcolepsy with cataplexy. In most other cases the hypocretin-1 level in the CSF is normal, suggesting another cause for the disorder.

Symptomatology

Narcolepsy with cataplexy may be referred to as narcolepsy type 1 and narcolepsy without cataplexy is referred to as narcolepsy type 2. However described, narcolepsy with or without cataplexy (hereafter ‘narcolepsy’) remains a clinically diagnosed disease with a constellation of symptoms:

Excessive Daytime Sleepiness (EDS)

EDS is the most common and disabling symptom of narcolepsy and is present in all patients with the disease. Sleepiness in narcolepsy is usually more severe than in other sleep disorders.

Sleepiness often becomes irresistible, resulting in inadvertent naps, even during activities such as talking, eating, standing, walking and driving in traffic, thus putting a heavy social burden on these patients (Dement et al. 1966, Dement 1976).

Cataplexy
Cataplexy is pathognomonic of the disease. It presents as a sudden but progressive, short lived, bilateral loss of muscle tone elicited by emotions such as laughter, elation, anger and surprise (Guilleminault 1976). It is usually associated with normal consciousness and awareness; respiratory and extra ocular muscles remain unaffected. Cataplexy probably represents the muscle atonia which normally occurs during REM sleep

Fragmented night-time sleep
In narcolepsy, a damaged sleep structure with abnormal, disrupted sleep patterns is manifested. Patients experience abnormal intrusions of SOREM periods and sometimes a greatly increased proportion of transitional Stage 1 sleep, while Stages 3 and 4 sleep may be significantly diminished. In addition, they suffer from frequent awakenings and frequent shifts between different sleep stages (Montplaisir et al. 1978). Typically, narcoleptic patients fall asleep almost instantly when they go to bed but their sleep is interrupted by frequent awakenings. Many patients report dreaming as soon as they fall asleep. Disturbed nocturnal sleep is present in approximately 50% of patients and can be very disabling. The recurrent night-time awakenings are associated with a feeling of restlessness during the night.

Ancillary symptoms
Sleep paralysis is an inability to move that occurs at sleep onset or upon awakening. Hypnogogic and hypnopompic hallucinations are dream-like visual or auditory perceptions that occur at sleep onset and upon awakening respectively. Automatic behaviours may occur without full awareness or memory, because of sleepiness or micro sleep. It is merely an indication of the severity of daytime sleepiness (Guilleminault et al. 1975)

Narcolepsy affects the social, mental and physical health of patients and has a significant negative impact on their physical and emotional wellbeing. It can be physically and socially disabling for patients.

Current Treatment of Narcolepsy
The current treatment of narcolepsy is aimed at alleviating the individual components of the symptom pentad of the narcoleptic disease: excessive daytime sleepiness, fragmented night-time sleep, cataplexy, sleep paralysis and hypnogogic hallucinations. There is however, no single treatment that has demonstrated ability to bridge all of the contributors to the condition and improve all the narcolepsy related symptoms, with the exception of sodium oxybate.

Pharmacotherapy for EDS has consisted primarily of the daytime administration of sympathomimetic stimulants, such as methylphenidate, and d-amphetamine to increase alertness and improve daytime performance. Unfortunately, tolerance to these agents develops in as many as 30% of patients, sometimes necessitating periodic “drug holidays.” Adverse events commonly include headaches, nervousness, irritability, tremor, insomnia, anorexia, gastrointestinal disturbances and palpitations. At high doses, the use of stimulants may be associated with

hypertension, myocardial ischemia and psychosis (Guilleminault 1993). The only recent advancement for the treatment of EDS in narcolepsy patients is modafinil (and its R- racemate armodafinil), chemically and pharmacologically unrelated to other stimulants, it has an improved adverse event profile and decreased abuse potential; however, its use rarely results in normal measures of EDS (U.S. Modafinil in Narcolepsy Multicenter Study Group 1998). Importantly, for modafinil, there are only data to support the use for narcoleptic patients demonstrating EDS; there are no effects on patients with cataplexy or for those experiencing problems with sleep continuity and architecture. The stimulants registered in Australia are summarised in Table 1.

Prior to the approval of sodium oxybate, the available treatment for the REM-related symptoms of narcolepsy were insufficiently tested (class III and class IV evidence studies only) and unapproved despite their widespread use. Pharmacotherapy consisted primarily of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). These medications suppress REM sleep and this property extends, to a limited extent, to the REM related symptoms of narcolepsy. They provided little, if any, benefit for disrupted night-time sleep. With respect to TCAs, adverse events are often related to their anticholinergic activity, resulting in dry mouth, tachycardia, blurred vision, constipation and urinary retention as well as non-anticholinergic effects, such as sexual dysfunction. Although the newer SSRIs demonstrate an improved adverse event profile, they are less efficacious than the TCAs. The abrupt discontinuation of agents in both drug classes may result in rebound cataplexy, representing a serious safety concern.

The availability of sodium oxybate represents a significant improvement over the REM-suppressing TCAs and SSRIs, providing significant reductions in cataplexy as well as trends suggesting important improvements in hypnogogic hallucinations and sleep paralysis. In addition, it provides significant improvements in EDS and fragmented night-time sleep, as well as other narcolepsy symptoms, without the development of tolerance.

Traditional pharmacotherapy for narcolepsy has not provided substantial benefit for disrupted nocturnal sleep (Rogers et al 1994).

In Australia no TCA or SSRI is approved for narcolepsy or any of the individual component symptoms of narcolepsy.

Table 1: The registered indications for stimulants

Class	Drug	Registered Indication	Effectiveness
Sympathomimetic stimulants	Methylphenidate AUST R	[Tradename] are also indicated for the treatment of narcolepsy. The symptoms include daytime sleepiness, inappropriate sleep episodes and rapidly occurring loss of voluntary muscle tone. [Tradename] is effective for symptoms of sleepiness but not for loss of voluntary muscle tone.	Treatment of EDS - in narcolepsy type 2 No benefit in cataplexy – stipulated in the indication.
	Dexamfetamine AUST R	Narcolepsy and hyperkinetic behaviour disorders in children	Narcolepsy type 2
	Pemoline	Not registered in Australia	
Other psychostimulants	Modafinil AUST R	To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy; To treat excessive sleepiness associated with moderate to severe chronic shift work sleep disorder where nonpharmacological interventions are unsuccessful or inappropriate; As an adjunct to continuous positive airways pressure (CPAP) in obstructive sleep apnoea/hypopnoea syndrome in order to improve wakefulness.	Treatment of EDS – in narcolepsy type 2 No benefit in cataplexy, fragmented night-time sleep
	Armodafinil AUST R	To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy; To treat excessive sleepiness associated with moderate to severe chronic shift work sleep disorder where nonpharmacological interventions are unsuccessful or inappropriate; As an adjunct to continuous positive airways pressure (CPAP) in obstructive sleep apnoea/hypopnoea syndrome in order to improve wakefulness.	Treatment of EDS – in narcolepsy type 2 No benefit in cataplexy, fragmented night-time sleep

The proposed orphan condition narcolepsy is intended to include patients with and without cataplexy (both narcolepsy type 1 and type 2), patients with EDS, sleep fragmentation and ancillary symptoms. Therefore the broadest patient population is proposed and no consideration of the plausibility of a sub-set of patients is required.

Background information on the product

The rationale for the use of sodium oxybate in the proposed indication is described in terms of the active ingredient, its pharmacological class and mechanism of action, as well as the scientific background on its use in narcolepsy.

Active, pharmacological class, mechanism of action

Sodium oxybate is the non-proprietary name for the sodium salt of gamma-hydroxybutyrate (GHB). Sodium oxybate is a central nervous system (CNS) depressant, pharmacotherapeutic group: Other Nervous System Drugs, ATC code: NO7XX.

Sodium oxybate is a central nervous system depressant which reduces EDS and cataplexy in patients with narcolepsy and modifies sleep architecture. The precise mechanism by which sodium oxybate produces an effect on narcolepsy is unknown, however sodium oxybate is thought to act by promoting slow (delta) wave sleep and consolidating night-time sleep. Sodium oxybate administered before nocturnal sleep increases Stages 3 and 4 sleep and increases sleep latency, whilst reducing the frequency of sleep onset REM periods (SOREMs). Other mechanisms, which have yet to be elucidated, may also be involved.

Scientific Background on the Use of Sodium Oxybate in Patients with Narcolepsy

Sodium oxybate has been investigated for nearly 40 years and has been studied clinically for the treatment of narcolepsy with cataplexy for approximately 25 years. Experimental work with GHB in humans began soon after its discovery. Its pronounced CNS depressant actions combined with relatively rapid onset, and short duration of action with low toxicity led to its use initially as an intravenous anaesthetic agent in the 1960s in Europe. However, due to its weak analgesic and poor muscle relaxant properties, and the emergence of agents with much shorter duration of action, sodium oxybate never achieved widespread usage as a general or adjunctive anaesthetic outside Europe. It remains on the market today in France, Germany, and Austria as an anaesthetic agent and sedative, and in Italy as an oral solution for the treatment of alcohol withdrawal and maintenance of abstinence. GHB was previously marketed in France between 1969 and 1975 by Cernep Synthelabo Laboratory as an over-the-counter (OTC) agent for insomnia. It was taken off the OTC market primarily because of the side effects: “gastric intolerance, effects on the nervous system and too sudden sleep induction.”

Later research examined sodium oxybate as a potential hypnotic for the treatment of insomnia. Electroencephalogram (EEG) studies documented changes in sleep architecture that occurred during sodium oxybate-induced sleep in normal individuals (Yamada et al. 1967, Metcalf et al. 1966, Liberson et al. 1969).

In humans, sodium oxybate consistently increased delta wave sleep without suppression of REM sleep, and reported increased REM efficiency while decreasing REM latency. A pilot study of sodium oxybate in five patients with insomnia (one of whom had narcolepsy) concluded sodium oxybate induced sleep, which was subjectively and indistinguishable from natural sleep based on EEG recordings (Mamelak et al. 1973). The authors stated that the only clinical limitation of this treatment was the short duration of action of sodium oxybate (approximately 2 to 3 hours).

The effects of sodium oxybate on sleep continuity and architecture were eventually applied to a group of narcolepsy patients. The night-time oral administration of sodium oxybate in three small uncontrolled trials demonstrated the same EEG patterns accompanied by substantial improvements in daytime narcolepsy symptoms (Broughton and Mamelak 1979, 1980; Mamelak and Webster 1981).

These improvements were shown to continue in patients treated with nightly sodium oxybate from 30 weeks (Scharf et al. 1985) to 9 years (Mamelak et al. 1986). In these early trials, sodium oxybate was well-tolerated. The ease of titrating sodium oxybate as a liquid formulation led to the development of individualized dosing that maximized therapeutic benefit while minimizing side effects. Furthermore, Mamelak anecdotally noted that divided doses were required for the treatment of narcolepsy symptoms. Discontinuation of dosing or taking only one dose resulted in the gradual recurrence of symptoms (Mamelak et al. 1986).

The apparent beneficial effects of nightly sodium oxybate administration to narcolepsy with cataplexy patients were subsequently supported by two randomized placebo-controlled studies. Collectively, these trials demonstrated that the nightly administration of sodium oxybate significantly increased combined Stages 3 and 4 sleep, and decreased sleep stage shifts and the number of night-time awakenings (Scrima et al 1990; Lammers et al. 1993). In addition, they produced varying degrees of improvement in daytime symptoms including a significant decrease in cataplexy attacks, hypnogogic hallucinations, inadvertent naps and the severity of subjective daytime sleepiness (Scrima et al. 1989; 1990; Lammers et al 1993). It was proposed (Scrima et al. 1990) that the therapeutic effect of sodium oxybate in the treatment of narcolepsy may result from a consolidation of nocturnal sleep, in part because the short half-life of the drug (approximately 1 hour) is too short to explain the significant effects seen on daytime symptoms.

In addition to subjective improvements in the severity of narcolepsy symptoms, there were other benefits as evidenced from studies where polysomography analysis was performed on patients before and after sodium oxybate treatment (Scharf et al 1985; Montplaisir et al 1986 Bedard et al 1989). These authors demonstrated decreased REM latency and increased REM efficiency from baseline to endpoint. The Montplaisir and Scharf studies showed that sodium oxybate increased the percentage of Stages 3 and 4 sleep. In addition, Montplaisir and Godbout (1986) showed a decrease in REM fragmentation and an increase in the percentage of REM sleep. Taken together, these studies indicate that sodium oxybate consolidates sleep architecture. The effective dose range in these trials was approximately 3 g to 9 g.

Clinical development

Sodium oxybate has been fully developed as a prescription/controlled medicine.

In addition to studies of pharmacokinetics (bioavailability, interaction studies, CYP450 effects), dose-proportionality and a taste test a full clinical program has been developed in narcoleptic patients.

Six randomized, double-blind placebo controlled trials have been carried out to support the effectiveness of sodium oxybate in the treatment of narcolepsy: OMC-SXB-22, OMC-SXB-15, OMC-GHB-2, OMC-SXB-21, Scrima, and Lammers. Additionally, five uncontrolled studies have been conducted: OMC-GHB-3, OMC-SXB-6, OMC-SXB-7, OMC-SXB-20 and OMC-SXB-19.

Of these trials, 4 controlled (OMC-GHB-2, OMC-SXB-21, Scrima, and Lammers) and 3 open non-comparative label trials (OMC-GHB-3, OMC-SXB-6, OMC-SXB-20) form the studies which support of the treatment of cataplexy in narcolepsy patients while 2 additional controlled trials (OMC-SXB-15, OMC-SXB-22) particularly support the treatment of EDS.

Sleep continuity and architecture variables were recorded and analyzed in all these trials and results are detailed to support beneficial effect of sodium oxybate on fragmented night-time sleep, another important symptom in narcolepsy.

Results from these trials demonstrate that sodium oxybate, at dosages between 3.0 g and 9.0 g per day is effective in improving subjectively (Epworth Sleepiness Scale (ESS) and objectively (Maintenance of Wakefulness Test (MWT)) measured EDS, the number of inadvertent naps during the day, reducing the frequency of cataplexy attacks, the subjectively and objectively PSG measured number of nocturnal awakenings, the patients quality of life (Functional Outcomes of Sleep Questionnaire (FOSQ), SF-36, Pittsburgh Sleep Quality Index (PSQI) as well as the investigator's overall impression of change in severity of disease (Clinical Global Impression of change (CGI-c).

A tabular summary of the trials is provided in Appendix 1.

Regulatory status

Sodium oxybate has not been registered, nor has orphan designation previously been applied for in Australia.

Orphan drug designation was sought and approved for the treatment of narcolepsy in both the EU (February 2003) and in the USA (November 1994).

Following orphan designation in the EU, UCB decided to submit a marketing authorisation application for a sub-population – “Treatment of cataplexy in patients with narcolepsy” as the initial submission in March 2004. A major (Type II) variation to extend the indication to “Treatment of narcolepsy with cataplexy in adult patients” was submitted and approved in 2007.

Currently sodium oxybate is registered throughout Europe (including Switzerland), the USA, Canada and Turkey.

Rationale for seeking a pre-submission meeting

The seriously debilitating nature of the condition is based on the serious impact that the disease can have on a patient's life. The deleterious impact of narcolepsy on quality of life is well established (Goswami, 1998; Daniels et al, 2001). Before and after diagnosis, narcoleptics experience unrelenting psychosocial stress, with different stresses affecting each decade of life.

Adolescents commonly report embarrassment, academic decline and loss of self-worth. Hypnagogic hallucination may lead individuals to question their own sanity and may be mistakenly diagnosed as schizophrenia. Adults face major concerns in the workplace and in interpersonal relationships. The effects of sleepiness and cataplexy have major effects on personal and public safety. Of particular concern is the risk of serious accidents at work or while driving. Severe cataplexy, resulting in immediate and sudden body collapse, can be dangerous and can occur so quickly that there is not time to prepare. Unless cataplexy can be controlled, many normal activities must be avoided.

Quality of life

Narcolepsy affects the social, mental and physical health of patients and has a significant negative impact on their physical and emotional well being (Goswami 1998). A postal survey of 305 patients in the UK reported that median scores in all eight domains of the Short Form 36 (SF-36) quality of life questionnaire were significantly lower than normative data (Daniels et al. 2001). In considering the quality of life of 481 narcoleptic patients as measured by the SF-36 questionnaire, these patients suffered quality of life domains that were as bad, or worse, than Parkinson's disease and epilepsy (Beusterien et al. 1999).

Socioeconomic impact

In a study evaluating the socioeconomic impact of narcolepsy in 75 German patients (54 with cataplexy, 21 without), 59% were unemployed and 43% of patients stated that their condition was the main reason for being out of work (Dodel et al. 2004). It is therefore clear that narcolepsy is physically and socially disabling for patients.

Existing therapies

The existing therapeutic goods with registered indication including narcolepsy (with or without cataplexy) include the sympathomimetic stimulants methylphenidate and dexamphetamine, which are primarily used to manage EDS. It is noted in the product information of methylphenidate (refer to Table 1) that the product is not effective for 'the loss of voluntary muscle tone', presumably cataplexy. Both modafinil and armodafinil (also psychostimulants, with a different mechanism) are indicated for EDS associated with narcolepsy.

Although antidepressants have been used to manage the REM-related symptoms of narcolepsy they are not registered for use in narcolepsy in Australia.

Therefore while only dexamphetamine and methylphenidate are indicated for 'narcolepsy' as first line treatments these medications are recognised as often being be inadequate to control EDS, not to be effective in cataplexy and do not influence sleep fragmentation. Furthermore

these agents have a range of potential side effects which at times make specific therapy intolerable. There remains an unmet need for patients to adequately control their condition.

Unment need
This unmet need has been identified by the ASA who in 2014 took it upon themselves to submit an application to have sodium oxybate rescheduled, and made several contacts with UCB Australia to explore the mechanisms to make Xyrem available to Australian patients.

UCB has been providing Xyrem under the Special Access Scheme (SAS) as a Category B medicine since month year.

Xyrem is not a core product to UCB, however, with the interest generated by the ASA and patients (some of whom have engaged with media and with the Department of Health) UCB wishes to explore orphan designation for the product and available means to facilitate registration.

2. Questions and Sponsor's Position

Prevalence data for narcolepsy

As there are no Australian prevalence data published for narcolepsy UCB have asked the ASA to provide information on the prevalence of narcolepsy in Australia. ASA reviewed the published epidemiology and prevalence publications for other countries and confirmed that the both the demographic details and diagnostic criteria used were in line with the Australian population and practices.

In addition the ASA provided information on audits of two large specialist sleep centres which support the prevalence of narcolepsy in Australia and being similar to that internationally (published data from USA, Europe, Hong Kong). Their data estimate that the prevalence of narcolepsy is 31.25 per 100,000 (or approximately 3 per 10,000; thus within the TGA orphan designation limit). This figure is the mean of prevalence rates across studies (where prevalence rates were provided for with or without cataplexy, a mid point of these 2 figures was used).

The ASA statement is attached as an Appendix to this briefing package.

Question 1:

Does the TGA agree that this approach to source confirmation that the international prevalence is appropriate, and that the Australian prevalence is consistent with international data?

TGA's response: The TGA does not believe that Narcolepsy represents a truly orphan indication given that, there are other drugs [Dexamphetamine, Modafinil, Armodafinil] on the Australia market already indicated for Narcolepsy (a chronic neurological disorder of excessive daytime sleepiness (EDS). *It may or may not occur with other symptoms such as cataplexy, sleep paralysis, fragmented night-time sleep and hallucinations).*

Given that:

- **the cohort of patients in the clinical dossiers evaluated for Dexamphetamine, Modafinil and Armodafinil experienced Narcolepsy, Cataplexy, disturbed nocturnal sleep patterns plus other paranormal sleep behaviours;**
- **all three drugs only had unqualified Narcolepsy (EDS) indication, despite the above;**
- **Narcolepsy indication for Dexamphetamine, Modafinil and Armodafinil was based on Category 1 Applications**

The TGA believes that:

- **a "head to head" trial assessing the superiority of UCB Xyrem over those already registered products for narcolepsy, will be more appropriate in terms of clinical evidence to justify UCB's implicit claim, that the effective treatment of the other "possible symptoms" associated with narcolepsy, such as catalepsy and fragmented night-time sleep, can only be provided by Xyrem.**
- **procedural fairness also needs to prevail in that, both the sponsors of Dexamphetamine, Modafinil and Armodafinil submitted Category 1 Applications to register the indication of Narcolepsy. Based on that, it is advisable and only fair that UCB also submits a Category 1 Application to register Xyrem in the treatment of Narcolepsy indication.**

Identification of existing therapeutic goods

Only 4 registered products have been identified which are indicated for 'narcolepsy' or for the treatment of EDS in narcolepsy. These are: methylphenidate, dexamphetamine, modafinil and armodafinil.

However, in the broadest understanding of narcolepsy, none of these 4 registered products is acknowledged to provide effective treatment of all of the symptoms, most particularly catalepsy and fragmented night-time sleep. Therefore the current treatment armamentarium is at times inadequate to control even EDS in the setting of maximal dosage and the range of potential side effects, which at times make therapy intolerable with existing agents.

In contrast, clinical trials with sodium oxybate have demonstrated efficacy in each of the three main symptoms of narcolepsy, and importantly the evidence of efficacy is as both a monotherapy and an adjunctive therapy (to eg modafinil) for patients with severe cases (including children) who may be on maximal doses of several conventional medications, and still have significant symptoms.

In comparison with other agents indicated for narcolepsy, sodium oxybate offers improved efficacy. In addition to its proven therapeutic effect on cataplexy (a component of the disease which is not effectively managed by other therapies), sodium oxybate is effective at alleviating the individual components of the narcoleptic disease. Sodium oxybate has been shown to significantly reduce the EDS associated with narcolepsy (both alone and in conjunction with stimulants), improve the overall clinical status of patients with narcolepsy, and improve the fragmented night-time nocturnal sleep associated with this disease.

Question 2:

Does the TGA agree that sodium oxybate offers a significant benefit – in improved efficacy for patients with narcolepsy, and that the proposed orphan indication ‘treatment of narcolepsy’ is intended to encompass a broader patient group than the existing products are registered for ?

TGA’s response: NO. The TGA requires properly conducted and well-designed, randomised clinical trial with active arm, demonstrating that only Xyrem has proven therapeutic effect on cataplexy (a possible component of the narcolepsy) which is not effectively managed by other registered drugs for narcolepsy.

Availability of EU dossier and evaluation reports to facilitate orphan registration

The EU submissions for sodium oxybate – both the initial MAA for treatment of cataplexy in patients with narcolepsy and the variation submitted to extend the indications to treatment of narcolepsy with cataplexy, would be the basis of an eCTD submission to the TGA. UCB will also try to identify the evaluation reports for these submissions.

The only differences between the original submissions [MAA (2003) and variation 2007] are:

- An updated Quality module (Module 3) – to include minor variations since the original MAA was approved
- Consolidation of the Clinical Overview and summaries (Module 2.5 and 2.7) with final reports in place of previously interim reports
- Conversion to an eCTD submission

Question 3:

Does the TGA consider that submission of the eCTD with the updates as presented would be acceptable and would there be benefits in providing the EU evaluation reports to facilitate evaluation ?

TGA response: Submission of the eCTD with the updates as presented would be acceptable. Provision of EU evaluation reports to facilitate a Category 1 application evaluation (NOT ORPHAN REGISTRATION) could be useful.

Appendix 1: Tabular listing of all clinical studies with sodium oxybate oral solution

Type of Study	Study Identifier	Objectives	Study design and control	Test product; regimen;route of administration	Number of subjects	Healthy subjects or diagnosis	Duration of treatment	Study status; report type
BA	OMC-SXB-11	To assess the effect of a high fat meal on the BA of sodium oxybate oral solution	Open, randomised, crossover study	Sodium oxybate oral solution 4.5 g as a single oral dose; fasting vs high fat meal	36 (34 evaluable)	Healthy subjects	Single dose	Complete full
IV	Covance 6627-129	To characterize the in vivo inhibitory potential of sodium oxybate on CYP450 isoenzymes.	N/A	Sodium oxybate at concentrations of 3, 10, 30, 100 and 300 µM	N/A	N/A	N/A	
IV	Covance 6627-150	To characterize the in vivo inhibitory potential of sodium oxybate on CYP450 isoenzymes.	N/A	Sodium oxybate at concentrations of 300, 1000 and 3000 µM	N/A	N/A	N/A	
PK	OMC-SXB-9	To assess PK< including dose proportionality	Open, randomised, two-period crossover study	Sodium oxybate oral solution 4.5 g (2 x 2.25 g) and 9 g (2 x 4.5 g)	13 (12 evaluable)	Healthy subjects	Single dose	Complete full
PK	OMC-SXB-8	To assess PK in males and females	Open label	Sodium oxybate oral solution 4.5 g	36	Healthy subjects	Single dose	Complete full
Taste	OMC-SXB-16	To compare placebo solutions with active solution with regard to taste	Blinded, placebo controlled	Sodium oxybate oral solution – 3 g swilled in mouth	12	Healthy subjects	Single dose	Complete full

Type of Study	Study Identifier	Objectives	Study design and control	Test product; regimen; route of administration	Number of subjects	Healthy subjects or diagnosis	Duration of treatment	Study status; report type
PK	OMC-GHB-4	To assess PK in patients on chronic treatment	Open	Sodium oxybate oral solution at total dose 6 g (2 x 3 g)	6	Narcoleptic patients	Single dose	Complete full
PK	OMC-SXB-10	To assess PK after single dose and 8 weeks of treatment in narcoleptic patients who had not previously received sodium oxybate	Opel label, two period study	Sodium oxybate oral solution at 4.5 g	13	Narcoleptic patients	Single dose	Complete full
PK Int	OMC-SXB-12	To assess any PK interaction between sodium oxybate and zolpidem	Open-label, three period, three treatment randomised crossover study	Sodium oxybate oral solution 3 g and 5 g zolpidem, alone and together	15	Healthy subjects	Single dose	Complete full
PK Int	OMC-SXB-14	To assess any PK interaction between sodium oxybate and protriptyline	Open-label, three period, three treatment randomised crossover study	Sodium oxybate oral solution 3 g and 5 g protriptyline, alone and together	12 (11 evaluable)	Healthy subjects	Single dose	Complete full
PK Int	OMC-SXB-17	To assess any PK interaction between sodium oxybate and modafinil	Open-label, three period, three treatment randomised crossover study	Sodium oxybate oral solution 3 g and 5 g modafinil, alone and together	13 (12 evaluable)	Healthy subjects	Single dose	Complete full
PK Int	OMC-SXB-24	To determine the effect of sub-chronic omeprazole on BA of sodium oxybate	Open-label, three period, three treatment randomised crossover study	Sodium oxybate oral solution 3 g alone or after omeprazole 40 mg once daily for 5 days	44 (42 evaluable)	Healthy subjects	Single dose	Complete full

Type of Study	Study Identifier	Objectives	Study design and control	Test product; regimen; route of administration	Number of subjects	Healthy subjects or diagnosis	Duration of treatment	Study status; report type
Efficacy / safety	OMC-GHB-2	To compare the efficacy and safety of three doses of sodium oxybate and placebo in the treatment of the symptoms of narcolepsy	Double-blind, randomised, parallel group, placebo controlled	Sodium oxybate oral solution at total doses of 3, 6 and 9 g (as 2 divided doses) and placebo taken nightly	136	Narcoleptic patients	4 weeks	Complete full
Efficacy / safety	Scrima	To compare the efficacy and safety of sodium oxybate and placebo in the treatment of the symptoms of cataplexy and with regard to effects on the PSG	Randomised, double-blind, placebo controlled crossover study	Sodium oxybate oral solution at 2 x 25 mg/kg at night, and matching placebo	20	Narcoleptic patients	29 days	Complete full
Efficacy / safety	Lammers	To compare the efficacy and safety of sodium oxybate and placebo in the treatment of the symptoms of cataplexy and with regard to effects on the PSG	Randomised, double-blind, placebo controlled crossover study	Sodium oxybate oral solution at 2 x 30 mg/kg at night, and matching placebo	25	Narcoleptic patients	4 weeks	Complete full
Efficacy / safety	OMC-SXB-21	To provide evidence for long-term efficacy of sodium oxybate based upon return of cataplexy symptoms on cessation of a minimum of 6 months of open label treatment	Double-blind, placebo controlled study	Sodium oxybate oral solution at 3, 4.5, 6, 7.5 or 9 g/day (in 2 divided doses) at night, and matching placebo	55	Narcoleptic patients	4 weeks	Complete full

Type of Study	Study Identifier	Objectives	Study design and control	Test product; regimen; route of administration	Number of subjects	Healthy subjects or diagnosis	Duration of treatment	Study status; report type
Efficacy / safety	OMC-GHB-3	To evaluate the safety and efficacy of sodium oxybate in chronic use	Long-term, open label non-randomised extension study (extension of OMC-GHB-2)	Sodium oxybate oral solution at starting dose of 6 g at night, titrated to effect at 3, 4.5, 6 or 9 g/day	117	Narcoleptic patients	24 months	Complete full
Efficacy / safety	OMC-SXB-6	To evaluate the safety and efficacy of sodium oxybate in long-term use	Open label study	Sodium oxybate oral solution at starting dose of 4.5 g at night, titrated to effect at 3, 4.5, 6, 7.5 or 9 g/day	185	Narcoleptic patients	6 month	Complete full
Efficacy / safety	OMC-SXB-7	To evaluate the safety and efficacy of sodium oxybate in long-term use	Long-term, open label non-randomised extension study (extension of OMC-GHB-3, OMC-SXB-6 or Scharf study)	Sodium oxybate oral solution at continued dose of 3, 4.5, 6 or 9 g/day	145 (interim)	Narcoleptic patients	24 months	Not complete, full (interim) and safety update reports
Safety	Scharf	To assess the safety of sodium oxybate in very long-term use (up to 16 y)	Retrospective compilation of safety data	Sodium oxybate oral solution at 3 to 9 g/night	143	Narcoleptic patients	Up to 16 years	Complete, safety
PD/ efficacy/ safety	OMC-SXB-20	To assess the effects of sodium oxybate on sleep architecture (by PSG) and narcolepsy symptoms and to assess safety	Open label study in which patients received increasing doses of sodium oxybate	Sodium oxybate oral solution at total doses of 4.5, 6, 7.5 and 9 g/day (in 2 divided doses) at night	25	Narcoleptic patients	10 weeks	Complete, full

Type of Study	Study Identifier	Objectives	Study design and control	Test product; regimen; route of administration	Number of subjects	Healthy subjects or diagnosis	Duration of treatment	Study status; report type
Efficacy / safety	OMC-SXB-15	To compare the effects and safety of sodium oxybate to placebo in the treatment of excessive daytime sleepiness (EDS) in narcolepsy	Randomised, double-blind, placebo controlled, parallel group multicenter study	Sodium oxybate oral solution at 4.5, 6 or 9 g/day, (divided dose) and matching placebo	353 enrolled, 285 randomised, 228 ITT, 206 completed	Narcoleptic patients	8 weeks	Complete full
Efficacy / safety	OMC-SXB-22	To compare the effects and safety of sodium oxybate and modafinil with placebo in the treatment of EDS in narcolepsy	Randomised, double-blind, double-dummy, placebo controlled, parallel group multicenter study	Sodium oxybate oral solution (or placebo) at 6 or 9 g/day, (divided dose) Modafinil (or placebo) tablet 200, 400 and 600 mg.day	278 enrolled, 231 randomised, 201 completed	Narcoleptic patients	8 weeks	Complete full
Efficacy / safety	OMC-SXB-19	To evaluate the efficacy and safety of sodium oxybate in patients with narcolepsy	Open-label multicenter study	Sodium oxybate oral solution at 4.5, 6 or 9 g/day, (divided dose)	185 enrolled		12 weeks	Not complete; Safety update report.

Appendix 2: Australasian Sleep Association position statement and guidelines, regarding the use of sodium oxybate in the treatment of narcolepsy

John Swieca, Hailey Meaklim, Arthur Teng, Margot Davey, Yasaman Djavadkhani, Ron Grunstein, Dev Banerjee & Garun Hamilton

Prevalence of Narcolepsy

Narcolepsy is a rare but serious disorder. This sleep-wake condition causes profound disturbance to sleep quality, daytime alertness, quality of life and mental health.

The estimated prevalence rate of narcolepsy in Western countries is approximately 30-50 per 100,000 people, but this rate varies according to study methodology, geography, and diagnostic criteria used (1-5). To our knowledge, there are no published epidemiologic studies describing prevalence rates of narcolepsy in Australia. Therefore, a review of prevalence rates of narcolepsy in countries with similar demographic profiles and diagnostic procedures to Australia was conducted (Table 1). The average prevalence rate of narcolepsy from these studies is 31.25 per 100,000 (or approximately 3 per 10,000; thus within the TGA orphan designation limit). This figure is the mean of prevalence rates across studies and where prevalence rates were provided for with or without cataplexy, a mid point of these two figures was used. These data provide evidence that narcolepsy is a rare disorder, in countries that have similar demographics to those found in Australia.

Within Australian specialist sleep centres; the prevalence rate of narcolepsy is more common than in the general population, as would be expected with a filtered population. Australian studies suggest a prevalence rate 3.05% (5/168) for new referrals to a busy specialist metropolitan sleep disorder centre in 2015 ([redacted], personal communication). This is consistent with a 1991 study suggesting a rate of diagnosis of narcolepsy of 2.5% (5/200) for new patient referrals to another private sleep disorder centre in Melbourne, Australia (6). Although narcolepsy is common in a specialist referral population, the general unfiltered population prevalence rate is substantially lower, as outlined above.

Table 1. Studies on the prevalence of narcolepsy with similar demographic and diagnostic method to Australia

Study Year and Author	Location and Population	Diagnosis method	Number diagnosed/ Number screened	Prevalence per 100,000 (95% CI if available)	Comments
1982 (7)	Italy Unselected patients admitted over 1 year to hospital aged 6-92 y	Questionnaire and sleep study	1/2518	40 (1-221)	Only inpatients

1994 (8)	Finland White twins aged 33-60 y	Screen, interview, sleep study, HLA	3/11,354	26 (5-77)	Finnish Twin Registry. White population. All three cases were dizygotic and discordant. All had cataplexy
1996 (9)	United Kingdom. Random sample aged 15 Y and over	Telephone system All with cataplexy	2/4927	40 (5-145)	Computerised expert system
2002 (10)	Minnesota, USA All ages	Medical Records 1. Narcolepsy with Cataplexy 2. Narcolepsy with or without cataplexy	1. 35/37,667 2. 55/97,667	1. 36 (25-50) 2. 56 (42-73)	Study based on medial care in a defined population, Olmsted County, MN, for 1960-1989
2002 (11)	Hong Kong, China Residents aged 18 – 68 y	Phone screen, interview, sleep study, HLA	3/9851	30 (6 - 89)	All had cataplexy. HLA negative in one case who had atypical cataplexy
2002# (12)	Five European Countries	Telephone system All with cataplexy	9/18980	47 (22-90)	Computerised expert system (Sleep EVAL Expert system, utilising ICSD diagnostic criteria for narcolepsy)
2017 (13)	Catalunya (Spain) Patients of 13 specialist centres and screening of the public health care system	Narcolepsy diagnosis on patient record, validated against Brighton Collaboration Case Definitions	381/7424754	5.2	Denominator is the population of Catalunya. Note the prevalence rate 3 – 14 times lower than those found in other countries
2016 (5)	United States of America Population based epidemiological study of active duty military personal	Narcolepsy was defined in 3 ways: (1) 2 diagnoses of narcolepsy within 6 months of each other, one made	1675 cases/ 1685398 non cases	14.6 – 27.3	Investigated narcolepsy increased incidence before and after novel pandemic

	between 2004-2013	by a sleep expert; (2) 2 diagnoses by any provider followed by a narcolepsy prescription within 14 days of last visit; and (3) procedure code for a sleep study followed by a narcolepsy diagnosis by a sleep expert within 6 months. Used (ICD-9-CM criteria)			influence in 2009
2009 (14)	King County, Washington DC 18 years and older	1) Required physician diagnoses of narcolepsy (with and without cataplexy). 2) Then patients had an interview and buccal scrapings for HLA confirmation	425/1,366,417	1) With cataplexy = 21.8 (18.8 to 24.8) Without cataplexy 30.6(27.6-33.5) 2) 15.3 (12.8 to 17.9)	Denominator was the population of King County. Multiple methods overlapping methods of diagnosis identification targeting both clinicians and patients.

Note: This table extends on the work of (4); HLA = hypocretin levels assessed in cerebrospinal fluid

The Australian experience with sodium oxybate for narcolepsy – Data from a single Australian centre

Sodium oxybate was included in Schedule 8 of the Poisons Standard in 2014 with specialist sleep disorder centres able to provide access to sodium oxybate for narcolepsy under specific circumstances (the Special Access Scheme, Category B). One of the largest private sleep clinics in Melbourne, Australia, started prescribing sodium oxybate under these strict regulations in 2015. A retrospective chart review of patients at this centre was conducted on patients commencing on sodium oxybate between April 2015-April 2016 to understand their experience (15).

Fourteen patients were commenced on sodium oxybate, and patients were diagnosed with narcolepsy with cataplexy (Narcolepsy Type 1)(n=6); narcolepsy without cataplexy (n = 6) (Narcolepsy Type 2) and idiopathic hypersomnia (n=2). The mean daily starting dose was 3 g. The mean daily dose at week 12 was 5.5 g. For those with Narcolepsy Type 1 and difficult cataplexy symptoms (n = 6), the mean number of cataplexy episodes per week reduced from 15.5 to 2. For a subset with paired Epworth

Sleepiness Score (ESS), mean ESS reduced from 16 to 10.5 – a very large reduction noting that the minimum clinically important difference is a reduction of 2 points (16). Thirteen of fourteen patients (93%) elected to continue sodium oxybate beyond 12 weeks, despite the high cost of the medication. It is important to note, the most common side effects were nausea and anxiety. 1 patient had to be started on anti-emetics and 2 needed adjustment of anxiolytic medications. 1 patient had to discontinue sodium oxybate due to lack of efficacy. To date, 31 patients have commenced on sodium oxybate at this practice (personal communication, [redacted])

This Australian series indicates that sodium oxybate is a helpful adjunct treatment for people with narcolepsy, for reducing mean number of cataplexy attacks and significantly improving excessive daytime sleepiness. Its utility is reflected in the ongoing usage of sodium oxybate in the majority of people commenced despite its expense

To date there has not been any Australian experience with using sodium oxybate in paediatric sleep medicine practice. Despite this, overseas experience suggests it is equally as effective as in adults.

References

1. Wijnans L, Lecomte C, de Vries C, Weibel D, Sammon C, Hviid A, et al. The incidence of narcolepsy in europe: Before, during, and after the influenza A(H1N1)pdm09 pandemic and vaccination campaigns. Vaccine 2013, Feb 6;31(8):1246-54.
2. Overeem S, Black JL, Lammers GJ. Narcolepsy: Immunological aspects. Sleep Med Rev 2008, Apr;12(2):95-107.
3. Ahmed I, Thorpy M. Clinical features, diagnosis and treatment of narcolepsy. Clin Chest Med 2010, Jun;31(2):371-81.
4. Longstreth WT, Koepsell TD, Ton TG, Hendrickson AF, van Belle G. The epidemiology of narcolepsy. Sleep 2007, Jan;30(1):13-26.
5. Lee RU, Radin JM. A population-based epidemiologic study of adult-onset narcolepsy incidence and associated risk factors, 2004-2013. J Neurol Sci 2016, Nov15;370:29-34.
6. Johns MW. Polysomnography at a sleep disorders unit in melbourne. Med J Aust 1991, Sep 2;155(5):303-8.
7. Franceschi M, Zamproni P, Crippa D, Smirne S. Excessive daytime sleepiness: A 1-year study in an unselected inpatient population. Sleep 1982;5(3):239-47.
8. Hublin C, Kaprio J, Partinen M, Koskenvuo M, Heikkila K, Koskimies S, Guilleminault C. The prevalence of narcolepsy: An epidemiological study of the finnish twin cohort. Ann Neurol 1994, Jun;35(6):709-16.
9. Ohayon MM, Priest RG, Caulet M, Guilleminault C. Hypnagogic and hypnopompic hallucinations: Pathological phenomena? Br J Psychiatry 1996,Oct;169(4):459-67.
10. Silber MH, Krahn LE, Olson EJ, Pankratz VS. The epidemiology of narcolepsy in olmsted county, minnesota: A population-based study. Sleep 2002, Mar 15;25(2):197-202.
11. Wing Y-K, Li RH-Y, Lam C-W, Ho CK-W, Fong SY-Y, Leung T. The prevalence of narcolepsy among chinese in hong kong. Ann Neurol 2002, May;51(5):578-84.

12. Ohayon MM, Priest RG, Zulley J, Smirne S, Paiva T. Prevalence of narcolepsy symptomatology and diagnosis in the european general population. Neurology 2002, Jun 25;58(12):1826-33.
13. Tió E, Gaig C, Giner-Soriano M, Romero O, Jurado M-J, Sansa G, et al. The prevalence of narcolepsy in catalunya (spain). J Sleep Res 2017, Nov 24.
14. Longstreth WT, Ton TGN, Koepsell T, Gersuk VH, Hendrickson A, Velde S. Prevalence of narcolepsy in king county, washington, USA. Sleep Med 2009, Apr;10(4):422-6.
15. Khoo J, Cunnington D, Swieca J, Ellender C. Retrospectiv cohort review of people with narcolepsy treqtment with sodium oxybate: An Australian experience. Journal of Sleep Research 2016 Oct 1; 25: 38-38.
16. Patel S, Kon SSC, Nolan CM, Barker RE, Simonds AK, Morrell MJ, Man WD-C. The epworth sleepiness scale: Minimum clinically important difference in obstructive sleep apnea. Am J Respir Crit Care Med 2017, Sep 29.