Scottish Medicines Consortium

sodium oxybate 500mg/ml oral solution (Xyrem®)

UCB Pharma Ltd No. (246/06)

10 March 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

sodium oxybate (Xyrem®) is not recommended for use within NHS Scotland for the treatment of cataplexy in adult patients with narcolepsy**.**

In two studies the median percent decrease in weekly cataplexy attacks ranged from 49% to 85% for the dose range included in the product licence.

However, the economic case for this product was not demonstrated.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

sodium oxybate 500mg/ml oral solution (Xyrem®)

Indication

Treatment of cataplexy in adult patients with narcolepsy.

Dosing information

4.5g/day oral, divided into two equal doses up to a maximum of 9g/day oral, divided into two equal doses. The first dose should be taken upon getting into bed and the second dose 2.5-4 hours later. Patients should eat at least several (2-3) hours before taking the first dose of sodium oxybate at bedtime.

UK launch date

13 February 2006

Comparator medications

Clomipramine is the only medicine, in addition to sodium oxybate, licensed in the UK for the treatment of cataplexy.

Cost of relevant comparators

Drug	Regimen	Cost per year (£)
sodium oxybate	**4.5-9g/day po**	**6570-13140**
clomipramine	10-75mg/day po	16-57
clomipramine SR (Anafranil®)	75mg/day po	115

po per oral

Cost for sodium oxybate obtained from the submission. Costs for clomipramine obtained from the eVADIS database (accessed on 9/1/06).

Summary of evidence on comparative efficacy

Sodium oxybate, the sodium salt of gamma hydroxybutyrate (GHB), 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. The precise mechanism by which sodium oxybate produces anti-cataplectic activity in patients with narcolepsy is unknown. Cataplexy, reported by approximately 75% of patients with narcolepsy, is an abrupt, reversible, decrease in muscle tone caused by emotion, such as laughter, elation or anger.

Two randomised placebo-controlled trials have been conducted to evaluate the efficacy of four doses of sodium oxybate in the treatment of cataplexy associated with narcolepsy.

The first study recruited 136 patients =18 years with narcolepsy diagnosed by polysomnogram within the previous 5 years and a current diagnosis of narcolepsy for at least 6 months based on criteria established by the American Sleep Disorders Association. Patients with coexisting causes of daytime sleepiness and sleep apnoea were excluded, as

were patients taking hypnotics, anxiolytics, antidepressants (for depression), antihistamines, clonidine or anticonvulsants. Patients with a history of psychiatric disorders and those at risk of substance abuse were also excluded. Patients on a stable dose of stimulant for the treatment of excessive daytime sleepiness could continue stimulant treatment and comprised 83% of patients recruited. Patients entered a 4-week period where any medications used to treat cataplexy were withdrawn, followed by a washout period of 5 days or five times the half life of the discontinued medication up to 28 days where daily diary use was initiated. A 14-21 day baseline period followed where patients recorded the frequency of cataplexy events, as well as other specified symptoms in the daily diary. Patients were required to have at least three cataplexy attacks per week during the last 2 weeks of the baseline period to enter the double-blind treatment period. Patients were then randomised to placebo or sodium oxybate 3g, 6g, 9g nightly taken as two equally divided doses at bedtime and 2.5-4 hours later for a period of 4 weeks. Analysis was planned using Analysis of Variance (ANOVA) on the change from baseline to endpoint on the intent-to-treat population as well as Analysis of covariance (ANCOVA) for the primary efficacy variable (change in frequency of cataplexy attacks) using the baseline value as the co-variate. No power calculation was provided. The trial was completed by 120 patients. At baseline the median frequency of weekly cataplexy attacks was 20.5, 20.0, 23.0 and 23.5 for the placebo, and sodium oxybate 3g, 6g and 9g groups respectively. The median percentage change in cataplexy attacks from baseline to endpoint, was -28%, -49%, -49% and -69% for the placebo, and sodium oxybate 3g, 6g and 9g groups respectively ($p=0.0529$ for 6g vs placebo and $p=0.0008$ for 9g vs placebo).

The second trial had similar inclusion and exclusion criteria to the first trial, and recruited 228 patients = 16 years with current symptoms of narcolepsy including cataplexy and excessive daytime sleepiness. The study design included a 14-day lead-in period where patients recorded narcolepsy symptoms and adverse events associated with current narcolepsy treatments. There followed withdrawal and washout periods as in the previous trial. Prior to entering the 14-day baseline period, patients were randomised to their eventual treatment dose and during the baseline period were required to have = 8 cataplexy attacks per week to enter the final phase. Daily diaries as in the previous trial were used to record cataplexy events as well as other symptoms of narcolepsy. Patients then entered the dose titration phase, which comprised 8 weeks in total. Following one week of treatment with either placebo or sodium oxybate 4.5g, patients on sodium oxybate were randomised to continue at a dose of 4.5g for the duration of the trial or receive sodium oxybate 6g. After a further week patients in the 6g group were randomised to continue at a dose of 6g for the duration of the trial or receive sodium oxybate 7.5g. After a further week patients in the 7.5g group increased their dose to sodium oxybate 9g for 5 weeks. All sodium oxybate doses were taken as two equally divided doses. The change in total number of weekly cataplexy events from baseline to end-point, was analysed using ANCOVA in the intent-to-treat population. The median frequency of weekly cataplexy attacks at baseline was 17.08, 17.0, 24.75 and 17.79 for the placebo, sodium oxybate 4.5g, 6g and 9g groups respectively. The median percentage changes in the number of cataplexy attacks per week (from baseline to endpoint) were -21.3%, -57.0%, -65.0% and -84.7% for the placebo, sodium oxybate 4.5g, 6g and 9g groups respectively ($p<0.003$ for all sodium oxybate groups vs placebo).

A 12-month open-label extension study included patients who were previously recruited to the first study and was designed to evaluate the safety and efficacy of sodium oxybate at doses between 3-9g nightly. One hundred and eighteen patients entered the open label extension and were initially treated with sodium oxybate 6g nightly. The investigator could increase or decrease the dose in 1.5g increments at 2-weekly intervals, according to clinical efficacy or adverse experiences. The number of patients included in the analysis at 12 months was 75. The number of cataplexy events recorded in patient diaries was compared to that recorded during the baseline period of the 4-week double blind trial. The number of cataplexy attacks

continued to fall over the study period and at 12 months the median change in number of cataplexy attacks was -23 (-93%) change from baseline.

A study to evaluate whether abrupt cessation of sodium oxybate results in withdrawal in patients on long-term (mean duration of treatment, 21 months) treatment was conducted in 55 patients entered into the open-label study, described previously. The primary efficacy variable was the change in the number of cataplexy attacks between baseline and endpoint and was analysed using ANCOVA. Cataplexy attacks in the placebo group increased by a median of 4.2 and 11.7 for week 1 and 2 respectively, and by 21.0 overall, compared with no median change in the sodium oxybate group. The authors noted that in the placebo treated patients cataplexy attacks increased gradually and concluded there was no evidence of rebound cataplexy.

Summary of evidence on comparative safety

In the first randomised controlled trial, adverse events believed to be related to sodium oxybate were nausea, vomiting, dizziness and enuresis. Ten out of the 16 patients who did not complete the study withdraw due to adverse events and all but one was considered to be mild or moderate in severity. In the second randomised controlled trial adverse events occurring with >5% incidence and with significantly greater frequency than placebo were nausea and dizziness.

In the withdrawal study, adverse events occurring in the placebo group included insomnia, dizziness and somnolence, reported in one patient each and anxiety in two patients. These were attributed to return of narcolepsy rather than a withdrawal syndrome. The summary of product characteristics (SPC) notes that, although the clinical trial experience with sodium oxybate in narcolepsy/cataplexy patients at therapeutic doses does not show clear evidence of a withdrawal syndrome, in rare cases, events such as insomnia, headache, anxiety, dizziness, sleep disorder, somnolence, hallucinations and psychotic disorders were observed after sodium oxybate discontinuation.

Summary of clinical effectiveness issues

Sodium oxybate has been shown to reduce the frequency of cataplexy attacks. However, in the pivotal study 83% patients continued to take a stimulant to control the symptoms of excessive daytime sleepiness and therefore in practice concomitant stimulants are likely to be required. In addition, the SPC warns that sodium oxybate has the potential to cause respiratory depression and questions whether concurrent stimulant use in clinical trials may have affected respiration during the night. Patients should be questioned regarding signs of CNS or respiratory depression and prescribers should be aware that sleep apnoea occurs in up to 50% of patients with narcolepsy.

Patients must take the second dose of sodium oxybate 2.5-4 hours after the first dose which is taken upon getting into bed. This dosing regimen may be problematic, although it has been noted that sleep disruption and frequent awakenings are present in patients with narcolepsy and therefore awakening in order to take the second dose may be manageable.

Summary of comparative health economic evidence

The manufacturer submitted a cost utility analysis of sodium oxybate compared to placebo. The estimation of the benefits was based on an assumption that the quality of life of patients with cataplexy is comparable to that of patients with type 1 diabetes. The cost per QALY was estimated to be £28,000.The strength of the economic study was that a cost utility analysis was attempted and that the results were calculated over a number of time horizons, as is appropriate for chronic conditions. A key weakness of the model was the lack of an appropriate comparator. However, it was stated in the submission that the utility gain from treatment was 0.07, so the gain over 4 years should be 0.28; however, the submission appeared to show a gain of 1.21 QALYs. The 'true' cost per QALY, therefore, is likely to be around £120,000 and the manufacturer has confirmed that this economic submission was flawed.

The manufacturer therefore submitted a second cost effectiveness analysis comparing sodium oxybate to placebo. Trial data, including the open-label extension study, were used to estimate a reduction in the number of cataplexy attacks as a result of using sodium oxybate. The manufacturer estimates the additional cost to be less than £10 per attack averted. However, this economic analysis still compares sodium oxybate to placebo and the benefits are now not expressed in terms of QALYs, so there is no way to judge whether this is good value compared to other uses of NHS resources.

Patient and public involvement

Patient Interest Group Submission – UK Association of Narcoleptics (UKAN)

Budget impact

The manufacturer predicts that the gross budget impact would be £126,000 in year 1, rising to £475,000 in year 5. These figures are based on the estimate that the number of patients receiving sodium oxybate in year 1 is 14, rising to 54 in year 5 There may be some medicines budget savings, although these are not quantified in the analysis. There is disagreement between these figures and the figures in the submission (800 to 2000 patients).

Guidelines and protocols

Guidelines on the diagnosis and management of narcolepsy in adults and children, published in December 2002, were developed by an independent multi-disciplinary working party based on widespread consultation with the medical community and patient representatives and a thorough review of the published literature. The guidelines were sponsored by Cephalon UK Ltd, the manufacturer of clomipramine and modafinil.

The Cochrane review, *Antidepressants for narcolepsy,* published in 2005 concludes that there is scarce evidence to recommend the use of antidepressant drugs to treat cataplexy.

Additional information

Sodium oxybate was designated an orphan medicinal product in February 2003.

UCB Pharma Ltd will manage the distribution of sodium oxybate under schedule II of the Misuse of Drugs Regulations 2001.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 24 February 2006.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

US Xyrem Multicenter Study Group. A randomized, double-blind, placebo-controlled multi center trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. Sleep. 2000: 25: 42-49.

Xyrem International Study Group. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. Sleep Medicine. 2005: 6; 415-421

US Xyrem Multicenter Study Group. A 12 month open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. Sleep 2003: 26; 31-35

US Xyrem Multicenter Study Group. The abrupt cessation of therapeutically administered sodium oxybate (GHB) does not cause withdrawal symptoms. Journal of Toxicology. Clinical Toxicology. 2003: 41; 131-135

US Xyrem Multicenter Study Group. Sodium oxybate demonstrates long-term efficacy for the treatment of cataplexy in patients with narcolepsy. Sleep Medicine 2004:5; 119-123