HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

10 May 2006

Xyrem 500 mg/mL, oral solution
Box of 1 bottle of 180 mL (CIP: 370 235-2)

Applicant: UCB Pharma

Sodium oxybate

List I
Narcotic: prescription limited to 28 days. Available on prescription subject to conditions specified in the Decree of 31 March 1999.
Medicinal product subject to annual prescription initially, to be prescribed only by neurologists and doctors working in sleep centres.
Repeat prescription not restricted.

Date of Marketing Authorisation: 13 October 2005

Date orphan drug status granted: 3 February 2003

Reason for request: inclusion on the list of medicines approved for hospital use.

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

sodium oxybate

1.2. Indications

Treatment of cataplexy in adult patients with narcolepsy.

1.3. Dosage

Treatment should be initiated and monitored by a doctor specialising in sleep disorders.

Because of the well-known risk of sodium oxybate misuse, the doctor should check for a patient history of abuse of medicinal products.

The recommended starting dose is 4.5 g/day of sodium oxybate (9 mL of Xyrem) to be split into 2 doses of 2.25 g (4.5 mL/dose). The dosage should be individually determined according to efficacy and tolerance, up to a maximum dosage of 9 g/day (18 mL) to be split into 2 identical doses of 4.5 g/dose; the dosage should be adjusted in stages of 1.5 g per day (i.e. 0.75 g/dose or 1.5 mL/dose). A minimum of 2 weeks is recommended between dosage increases. The dosage of 9 g/day should not be exceeded because of the possibility of severe symptoms occurring at doses of 18 g/day or more.

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

Food reduces the bioavailability of sodium oxybate, so patients should take meals at least a few hours (2-3 hours) before the first dose of sodium oxybate. Patients should always wait the same length of time between their meal and taking the treatment.

Using Xyrem
Xyrem should be taken by mouth at bedtime and again 2.5–4 hours later.

Discontinuing treatment with Xyrem
The effects of discontinuing sodium oxybate therapy have not been systematically assessed in controlled clinical trials.
If the patient discontinues treatment for more than 14 consecutive days, therapy should be restarted at the lowest dose.

Patients with hepatic failure
The starting dose should be reduced by half in patients with hepatic failure and the effects of each dosage increase should be carefully monitored.

Patients with renal failure
Patients with renal failure should follow dietary guidelines to reduce their sodium consumption.

Elderly subjects
Elderly patients treated with sodium oxybate should be monitored for motor function and cognitive disorders.

Children and adolescents
Safety and efficacy in children and adolescents have not been established, and use in patients under 18 is not recommended.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

N : Central nervous system
N07 : Other CNS drugs
N07X : Other CNS drugs
N07XX : Other CNS drugs
N07XX04 : Hydroxybutyric acid

2.2. Medicines in the same therapeutic category

Xyrem is the only medicine with the indication “treatment of cataplexy in adults with narcolepsy”.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The efficacy of sodium oxybate against cataplexy has been assessed in two placebo-controlled trials (OMC-GHB-2[1] and OMC-SXB-21[2]) in narcoleptic patients with cataplexy.

These two trials tested daily doses of sodium oxybate 3–9 g, divided into two identical night-time doses. Before randomisation, anticataplectic treatments were withdrawn, while CNS stimulants (for sleep attacks) were continued in 85% of patients.

The 4-week trial OMC-GHB-2 was conducted in 136 adult patients (mean age 43.1) with narcolepsy (defined according to American Sleep Disorders Association criteria) for more than 6 months, and with moderate to severe cataplexy (3 or more attacks per week; median: 21 episodes/week) during the reference period. Patients were randomised to either placebo, or Xyrem 3 g/day, 6 g/day or 9g/day, divided into two identical night-time doses (the first at bedtime and the second 2.5–4 hours later).

The 2-week trial OMC-SXB-21 was specifically conducted to assess continued efficacy of Xyrem after long-term treatment. Fifty-five cataplectic patients previously treated with open-label Xyrem for 7–44 months were enrolled in this trial. To be included, patients had to be stable on Xyrem for at least 6 months (mean 21 months). Patients were randomised to continue on Xyrem at their stable dosage, or to placebo.

In both trials, the main efficacy endpoint was frequency of cataplexy attacks.

[1] US Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. Sleep 2002;25: 42-9.
[2] US Xyrem Multicenter Study Group. The abrupt cessation of therapeutically administered sodium oxybate (GHB) does not cause withdrawal symptoms. J Toxicol Clin Toxicol 2003;41:131-5.

Results

Change in number of cataplexy attacks after 4 weeks of treatment (ITT ANCOVA – ANOVA analysis)

	Number of patients	Median number of attacks per week		
		Reference period	Difference compared to reference period	P versus placebo ANCOVA/ANOVA
Trial OMC-GHB-2				
Placebo	33	20.5	- 4.3	
Xyrem 3.0 g/day	33	20.0	- 7.0	0.5235 / 0.5541
6.0 g/day	31	23.0	- 9.9	0.0529 / 0.0451
9.0 g/day	33	23.5	- 16.1	0.0008 / 0.0016
Trial OMC-SXB-21				
Placebo	29	4.0	21.0	
Xyrem	26	1.9	0	0.001

In the trial OMC-GHB-2, the investigators assessed overall improvement using CGIc (Clinical Global Impression of change). An overall improvement ("much improved" to "very much improved") was seen only at the 9 g daily dosage (80% vs. 18% in the placebo group).

In the trial OMC-SXB-21, the number of cataplexy attacks during the reference period differed by group. Doses of 6–9 g/day had similar effects; no effect was observed in patients treated with doses below 6 g/day.

Long term efficacy

Of 136 patients included in trial OMC-GHB-2, 117 were enrolled in a 12-month open-label extension trial (OMC-GHB-3). The efficacy of Xyrem was also assessed in a 6-month open-label trial at doses of 3–9 g per day in 185 patients (trial OMC-SXB-6). Patients in these two trials were enrolled in a further 2-year open-label long-term follow-up trial (OMC-SXB-7) (ongoing). An interim analysis of this trial covered 145 of the 300 patients expected to be included.

The results of these trials supported continued long-term efficacy (12 months follow-up) and suggested that response increases with duration of treatment.

3.2. Undesirable effects

In total, 421 patients were treated with sodium oxybate for a mean duration of 219 days (median 174 days, i.e. 6.5 months).

The safety profile of Xyrem is dosedependent. The undesirable effects most often reported were sleep disorders, dizziness, nausea and headache, occurring in 10–25% of patients.

Serious undesirable effects (such as acute confusional state, agitation, suicide) occurred in 4% of patients treated with Xyrem, compared with 1% in the placebo group. In the Xyrem group, 10% of patients discontinued treatment because of poor tolerance, compared with 1% of placebo group patients.

Frequency of undesirable effects (SPC)

- Common undesirable effects (≥ 1/100 – < 1/10)
Hypersensitivity, anorexia, abnormal dreams, abnormal thoughts, confusion, disorientation, nightmares, sleepwalking, depression, hallucination, agitation, sleep paralysis, somnolence, tremor, amnesia, blurred vision, vomiting, abdominal pain, diarrhoea, sweating, rash, muscle cramps, enuresis, asthenia, fatigue, feeling drunk, raised blood pressure.

- *Uncommon undesirable effects (≥ 1/1000 – < 1/100)*
Psychosis, paranoia, myoclonus, convulsions, faecal incontinence, urticaria.

- *Rare undesirable effects (≥ 1/10000 – < 1/1000)*
Respiratory depression.

- *Effects of withdrawal of treatment*

After discontinuing treatment, some patients had more frequent cataplexy attacks than before sodium oxybate therapy, but this may have been due to the variability of the disease. Clinical use of sodium oxybate in therapeutic doses in narcoleptic/cataplectic patients does not show clear evidence of a withdrawal syndrome. However, in rare cases, undesirable effects such as insomnia, headaches, anxiety, dizziness, sleep disorders, somnolence, hallucinations and psychotic disorders were seen on discontinuing therapy.

Xyrem is marketed subject to a risk management plan to monitor aspects of safety in use, notably the risk of respiratory depression, potential rebound and withdrawal effects, and risks of abuse or misuse.

3.3. Conclusion

The efficacy of Xyrem against cataplexy was assessed in a controlled trial (OMC-GHB-2) in 136 adult patients (mean age 43.1) with narcolepsy and moderate to severe cataplexy (median: 21 episodes per week). Daily doses of Xyrem tested were 3–9 g, divided into two identical night-time doses, for 4 weeks. Under these conditions, Xyrem produced a dose-dependent decrease in the frequency of cataplexy attacks (median decrease of -7, -10 and -16 respectively at daily doses of 3 g, 6 g and 9 g, compared with -4 in the placebo group; $p<0.05$ at doses of 6 g and 9 g/day). The maximum effect occurred only at the maximum recommended dose (9 g/day). Similarly, a significant improvement in patients' condition ("much improved" to "very much improved"), assessed by an investigator using CGIc (Clinical Global Impression of change), was observed only at the maximum dose (80% compared with 18% in the placebo group).

The results of a controlled short-term trial (OMC-SXB-21) and open-label trials of long-term use (up to 12 months) support continued efficacy of Xyrem in the long term, and also suggest that response increases with the duration of treatment. However, larger-scale long-term trials are necessary to prove this probable but not clearly demonstrated benefit.

The effects of discontinuing Xyrem therapy have not been systematically assessed in controlled clinical trials. The SPC includes a warning on discontinuing therapy: cataplexy episodes may occur more frequently and a withdrawal syndrome may occur.

The safety profile of Xyrem is dose-dependent. Attention should be drawn to the narrow safety margin between the maximum recommended dose of 9 g/day, and the 18 g dose which produces toxic effects. The most common undesirable effects were sleep disorders, dizziness, nausea and somnolence. Xyrem can also cause respiratory depression.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Narcolepsy is a chronic, mildly to severely disabling disease. It is considered to be an orphan disease as regards the number of patients affected. Cataplexy is one of the main symptoms of narcolepsy. It consists in a sudden loss of muscle tone that does not affect consciousness. Cataplexy attacks increase the risk of serious accidents in narcoleptic patients and are regarded as one of the two most disabling symptoms of narcolepsy.

Xyrem is a symptomatic therapy that reduces the frequency of cataplectic episodes in narcoleptic patients.

It is first line therapy.

The efficacy/safety ratio of Xyrem is substantial.

Public health benefit

Cataplexy is a condition that may be serious, severely impairing quality of life for some sufferers. The subpopulation requiring medical management is nevertheless a low burden on public health.

The therapeutic management of cataplexy would benefit from being standardised and improved. Although important for the subpopulation concerned, such improvement is not a public health priority.

In view of the data on managing cataplectic patients, the results of clinical trials with Xyrem and other therapies, and the question of whether these results would be the same in clinical practice, there is not sufficient evidence to suggest that Xyrem should be expected to improve the health of the cataplexy patient population.

Xyrem is therefore not expected to benefit public health.

The actual benefit of Xyrem is substantial.

4.2. Improvement in actual benefit

The Committee considered that Xyrem offers a minor improvement in actual benefit (IAB IV) in the usual management of cataplexy in adult patients with narcolepsy.

4.3. Therapeutic use

Narcolepsy symptoms require strictly regulated medical treatment.

- sleep attacks: therapy is based on lifestyle adjustments (scheduled naps) and medical treatment. First-line medical therapy relies on stimulating drugs such as modafinil (Modiodal). If Modiodal is ineffective, methylphenidate (Ritalin or Concerta) is prescribed.

- cataplexy attacks: depending on the frequency of episodes, different approaches may be tried: no active therapy (if patients have few symptoms, and their cataplexy is mild and generally partial), or medical therapy.

There is a professional consensus for medical therapy based on the empirical use of serotoninergic or tricyclic antidepressants, whose efficacy is poorly documented[3,4], and which have no Marketing Authorisation for this indication. At present Xyrem is the only medicine with a Marketing Authorisation for this indication. Although its mechanism of action is unknown, placebo-controlled trials have shown Xyrem to be effective in reducing the number of cataplexy attacks, with a continued long-term effect.

4.4. Target population

The target population for Xyrem is that of the adult population with narcolepsy that is subject to cataplexy attacks that are common and severe enough to need treatment.

The estimated prevalence of narcolepsy is 50 per 100 000 inhabitants[5,6,7].

This disease is widely underdiagnosed, probably for two reasons:
- the symptoms of narcolepsy are poorly identified by nonspecialist doctors and can be confused with the symptoms of other more common diseases;
- patients whose symptoms are mild and not very disabling do not seek treatment.

It is generally estimated that only about 20% of narcolepsy sufferers are diagnosed[8].

The prevalence of cataplexy in narcolepsy patients varies from 70–90% according to the literature. However, only 30% of patients with narcolepsy have cataplexy attacks that are common and severe enough to need treatment[9].

In this context, the estimated target population is 1800 patients at most.

4.5. Transparency Committee Recommendations

The Committee recommended inclusion on the list of medicines approved for use by hospitals and various public services for the indications and at the doses given in the Marketing Authorisation.

The Committee noted that Xyrem is marketed subject to a risk management plan to monitor aspects of safety in use, notably the risk of respiratory depression, potential rebound and withdrawal effects, and risks of abuse or misuse.

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[3] Vignatelli L, D'Alessandro R, Candelise L. Antidepressant drugs for narcolepsy (Reviews). The Cochrane Collaboration. *The Cochrane Library* 2006, Issue 2.

[4] Houghton WC, Scammell TE, Thorpy M. Pharmacotherapy for cataplexy. Sleep Medicine Reviews 2004;8:355-366.

[5] Ohayon MM *et al*. Prevalence of narcolepsy symptomatology and diagnosis in the European general population; Neurology 2002;58:1826-1833.

[6] Référentiel National – Collège des Enseignants de Neurologie – Version du 30/08/02

[7] Dement WC, Zarcone V, Varner V *et al*. The prevalence of narcolepsy. Sleep Res 1972;1:148.

[8] Overeems S, Mognot E, Van Dijk JG, Lammers GJ. Narcolepsy: Clinical features, new pathological insights and future perspectives. J Clin Neurophysiol 2001;28:78-105

[9] European public assessment report. EMEA. Scientific Discussion. Xyrem. *INN: Sodium oxybate - Published 22/11/05 Available from: http://www.emea.eu.int/humandocs/Humans/EPAR/xyrem/xyrem.htm*