London, 1 March 2007
Product name: Xyrem
Procedure No. EMEA/H/C/593/II/01

SCIENTIFIC DISCUSSION

1. Introduction

Narcolepsy fulfils the criteria for the classification as an Orphan Disease within the European Union (EMEA/14222/00 "Procedures for Orphan Medicinal Product Designation: General Principles"). Sodium oxybate was granted Orphan Drug Designation by the European Commission in February 2003.

Sodium oxybate is the non-proprietary name for the sodium salt of gamma-hydroxybutyrate (GHB), a naturally occurring compound that usually exists as either the free acid or the sodium salt. Sodium oxybate is a central nervous system depressant (Pharmacotherapeutic group: Other Nervous System Drugs, ATC code: NO7XX04). On 13 October 2005, the EU Commission Decision was issued for its marketing authorisation, for the indication "*Treatment of cataplexy in adult patients with narcolepsy*".

This indication statement has a focus on cataplexy. Cataplexy is, however, a key feature of narcolepsy, but not the only one. With this type II variation procedure, the MAH applied for an extension of the originally approved indication, to broaden its scope and encompass the full narcolepsy syndrome.

2. Clinical aspects

2.1 GCP

The Clinical trials were performed in accordance with GCP, as stated by the MAH. In addition, the MAH confirmed that the ethical requirements of the clinical trial directive 2001/20/EC were applied for clinical trials conducted outside the EU.

2.2 Clinical Efficacy

To broaden the scope of the originally approved indication to encompass the full narcolepsy disease, in practice, would mean to demonstrate an effect in daytime somnolence, as the other components of the syndrome are somnographic. Once an effect in cataplexy has been demonstrated, the most frequent clinical variable remaining to investigate would be Excessive Daytime Sleepiness (EDS), measured by the Epworth Sleepiness Scale (ESS). The Epworth Sleepiness Scale measures the likelihood of somnolence on a scale of 0-3 in eight everyday situations and has a maximum score of 24. In this scale, a score of 10 or lower is considered normal. Patients with narcolepsy usually have scores of 13 and above (representing moderate to severe sleepiness). A score of 18 or more is considered high sleepiness.

Data already assessed as part of the original Marketing Authorisation Application (MAA) submission partly contribute to support the broadened indication applied for with this procedure, but two new trials were also conducted and the resulting data were submitted with this application. In addition to presenting data emerging from the two new clinical studies (OMC SXB 15 and OMC SXB 22, see below), the MAH submitted also a complete analysis of the data emerging from all studies to date. This across-trial analysis consisted of pooled analysis and meta-analysis. The effects on Inadvertent Naps, Changes in Sleep Architecture, Subjective Number of Awakenings per Night, and Patient Assessment of Sleep Quality were presented.

The following table summarises all data available (old and new).

Table 1: Summary of Controlled and Uncontrolled Efficacy Studies

Trial Type	Trial Name	Primary Endpoint	Secondary Endpoints	TCAs/SSRIs Allowed?	Stimulants Allowed?
Controlled Trials	OMC-SXB-15	EDS (Epworth), CGI-c	MWT, cataplexy, sleep attacks, awakenings, hypnagogic hallucinations, sleep paralysis, FOSQ, SF-36, PSG	No	Stable dose
	OMC-SXB-22	EDS (MWT)	CGIc, Epworth, sleep attacks, PSQI, PSG	Yes	Modafinil only
	OMC-SXB-21	Cataplexy after sodium oxybate Withdrawal	None	No	Stable dose
	OMC-GHB-2	Cataplexy	Partial/complete cataplexy, hypnagogic hallucinations, sleep paralysis, Epworth, sleep attacks/inadvertent naps, night awakenings, total sleep, CGIc	No	Stable dose
	Lammers	Cataplexy, global impression (physician and patient)	MSLT, Sleepiness, REM/non-REM sleep	Yes	Yes
	Scrima	Cataplexy, MSLT	PSG, myoclonus, respiration, sleep onset REM, mood	No	Methylphen-idate
Uncontrolled Trials	OMC-SXB-20	PSG	EDS (Epwoth), MWT, Narcolepsy Symptoms	No	Stable dose
	OMC-SXB-6	Cataplexy, Narcolepsy symptoms	None	Yes	Yes
	OMC-GHB-3	Cataplexy	Partial/ complete cataplexy, hypnagogic hallucinations, Epworth, night awakenings, sleep paralysis, quality of nighttime sleep, sleep attacks/inadvertent naps, total sleep, CGIc	No	Stable dose

CGIc Clinical global impression of change
EDS Excessive daytime sleepiness
FOSQ Functional Outcomes of Sleep Questionnaire
MSLT Multiple sleep latency test
MWT Maintenance of Wakefulness Test
PSG Polysomnographic evaluation of sleep architecture
PSQI Pittsburgh Sleep Quality Index;

Brief Summary of Controlled trials

- OMC-SXB-15 (see below for full description)
- OMC-SXB-22 (see below for full description)
- OMC-GHB-2 was a randomized, double-blind, placebo-controlled comparison of 3, 6 and 9 g/d of sodium oxybate versus placebo in 136 patients treated for 4 weeks.
- OMC-SXB-21 was a randomized, long-term, double-blind, placebo-controlled study to compare continued sodium oxybate (3, 4.5, 6, 7.5 or 9 g/d in two divided doses) with placebo in 55 patients over a 2-week treatment period following long-term sodium oxybate treatment.
- The Scrima trial was a randomized, double-blind, placebo-controlled, crossover comparison of sodium oxybate (2 x 25 mg/kg/d) and placebo in 20 patients treated for 29 days.
- The Lammers trial was a randomized, double-blind, placebo-controlled, crossover comparison of sodium oxybate (2 x 30 mg/kg/d) and placebo in 25 patients treated for 4 weeks.

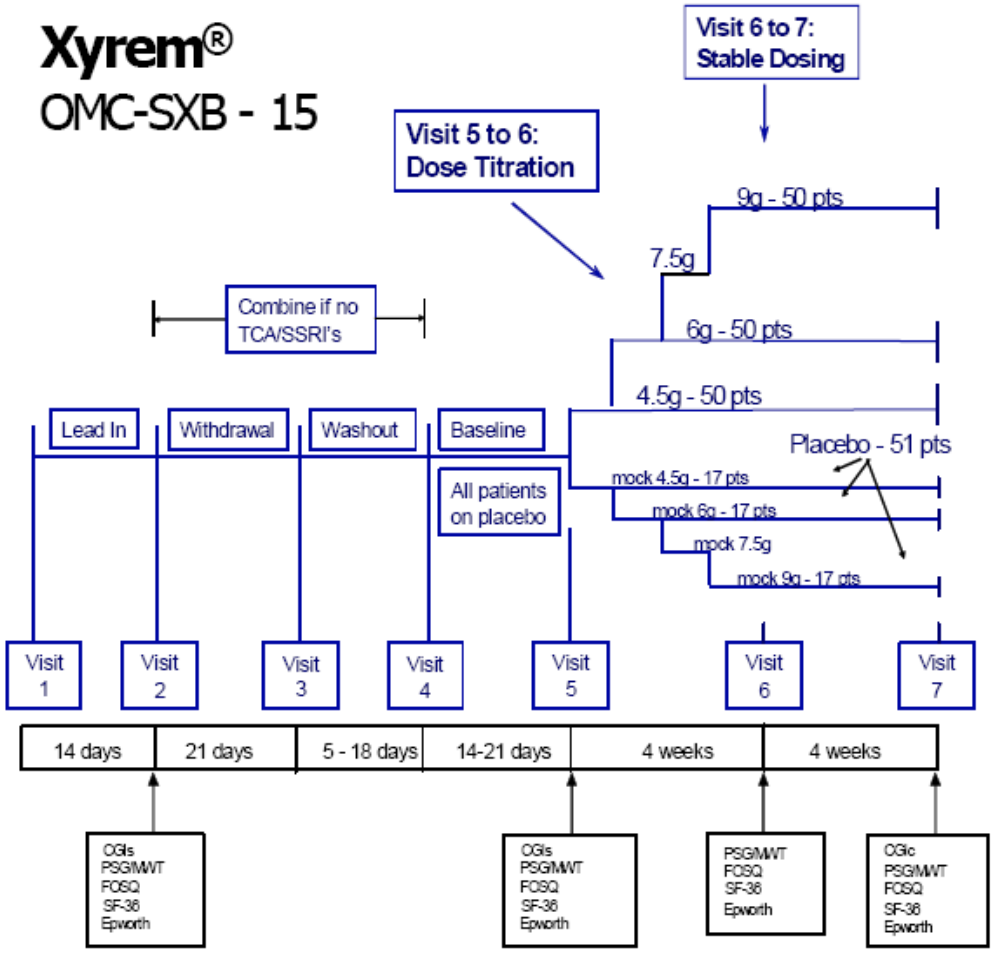
The clinical efficacy programme for this application was, however, based on the two Clinical Trials novel to this application (OMC SXB 15 and OMC SXB 22). The main focus of this Assessment Report is therefore on these two trials, which were designed to confirm the beneficial effects of sodium oxybate on EDS observed in the previously submitted clinical trials and to demonstrate that

these effects were associated with changes in sleep continuity and architecture. The two new studies differed from each other in antidepressant use. In OMC-SXB-15, these drugs were withdrawn, while in OMC-SXB-22, use of antidepressants for any purpose (not just for effects on cataplexy) was continued at stable dose. Both studies OMC-SXB-15 and OMC-SXB-22 were designed to establish the effects of sodium oxybate on EDS. Each of these studies used both the ESS and the MWT (Maintenance of Wakefulness Test).

- **Study OMC-SXB-15**

OMC-SXB-15 was a randomized, double-blind, placebo-controlled, parallel-group comparison of three dosages of sodium oxybate (4.5, 6 and 9 g/d) with placebo in 246 patients treated for narcolepsy for 8 weeks.

Figure 1: Schematic of the Study Design – OMC-SXB-15



Objectives

In OMC-SXB-15, patients were randomized to treatment with placebo or sodium oxybate at doses of 4.5, 6 or 9 g/d, following washout of previous antidepressants and other medications taken for cataplexy and a single-blind period on placebo. Patients assigned to 4.5 g began at that dose, but those assigned to 6 g or 9 g were titrated to their final dose. The primary measures of efficacy in the trial were changes in Excessive Daytime Sleepiness (EDS) as measured by the ESS, and change in the overall severity of the patient's narcolepsy symptoms as assessed blindly by the investigator using the CGI-c measure. Secondary measures of efficacy were changes in EDS as measured by the MWT, changes in the average number of cataplexy attacks per week (as recorded in patient diaries), number of inadvertent naps and effects on the PSG.

Sample size

A total of 401 patients were screened and 353 patients were enrolled. Of this latter number, 285 were randomly assigned to treatment. The All Treated Population included 246 patients who received at least one dose of double-blind medication. The Intent-to-treat (ITT) Population included 228 patients who received at least one dose of double-blind medication and had efficacy data at baseline Visits 6 and/or 7. The ITT population included 4 groups: placebo (59 patients), Xyrem 4.5 g/d (64 patients), Xyrem 6.0 g/d (58 patients), and Xyrem 9.0 g/d (47 patients).

Statistical Methods

When the clinical data sets were not normally distributed, non-parametric tests were used for analysis. Results have been expressed as medians when data are not normally distributed. The change from baseline within a group and the change from baseline between groups were tested. Samples sizes were based on the primary endpoints. Significance levels were adjusted for multiple testing, as required.

Results

The primary measures of efficacy were changes in excessive daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS), and the change in the overall severity of the patient's narcolepsy symptoms as assessed by the investigator using the Clinical Global Impressions of Change (CGI-c) measure. These results are summarised in tables 1 and 2 below.

Table 1 Summary of ESS in Trial OMC-SXB-15

Epworth Sleepiness Scale (ESS; range 0-24)				
Dose Group [g/d (n)]	Baseline	Endpoint	Median Change from Baseline	Change from Baseline Compared to Placebo **(p-value)**
Placebo (n = 60)	17.3	16.7	-0.5	-
4.5 (n = 68)	17.5	15.7	-1.0	0.119
6 (n = 63)	17.9	15.3	-2.0	**0.001**
9 (n = 55)	17.9	13.1	-2.0	< **0.001**

Table 2 Summary of CGI-c in Trial OMC-SXB-15

Clinical Global Impressions of Change (CGI-c)		
Dose Group [g/d (n)]	Responders* N (%)	Change from Baseline Compared to Placebo **(p-value)**
Placebo (n = 60)	13 (21.7)	-
4.5 (n = 68)	32 (47.1)	**0.002**
6 (n = 63)	30 (47.6)	< **0.001**
9 (n = 55)	30 (54.4)	< **0.001**

* The CGI-c data were analysed by defining responders as those patients who were very much improved or much improved.

In trial OMC-SXB-15, all doses of sodium oxybate were associated with a significant reduction in ESS from baseline but the reduction at the lowest dose used, 4.5 g/d, was not statistically significantly different from the (non-significant) decrease observed with placebo. The 6 g dose did not increase MWT significantly, but both the 4.5 g and the 9 g/d dose did; however, only the 9 g dose led to a significantly greater increase in MWT than was observed with placebo.

In agreement with the effects of sodium oxybate shown by the ESS Scale and the MWT, sodium oxybate treatment was also associated with improvements in the number of inadvertent naps in patients (see table 3 below). Study OMC-SXB-15 provided evidence of a dose-response effect on inadvertent naps. In this trial, the reduction in the number of inadvertent naps from baseline was statistically significant at all active doses, but the reduction was significantly different from that in the placebo group only at doses of 6 and 9 g/day and not 4.5 g/day.

Table 3 - Reduction in Number of Inadvertent Naps/Sleep Attacks in OMC-SXB-15

OMC-SXB-15 (median naps/attacks / week)					
	Baseline	Endpoint	Change	P-value for within-group change from baseline	P-value versus placebo for change from baseline
Placebo (n = 58)	13.96	12.50	-1.08	0.215	—
4.5 g/d (n = 62)	15.15	13.50	-2.96	**<0.001**	0.099
6 g/d (n = 57)	18.00	13.00	-6.50	**<0.001**	**<0.001**
9 g/d (n = 45)	14.00	8.50	-6.00	**<0.001**	**0.002**

In OMC-SXB-15, the Clinical Polysomnography (PSG) assessments of sleep continuity and architecture showed that groups treated with sodium oxybate 6 g/d and 9 g/d had clinically and statistically significant prolongation of Stages 3 and 4 sleep and associated increases in delta activity and in non-REM sleep duration. The most restorative components of sleep were thus improved.

With regards to Night-time Awakenings, in OMC-SXB-15, the administration of sodium oxybate improved the continuity of nocturnal sleep by significantly decreasing the number of objectively measured nocturnal awakenings. This effect was statistically significant at the 6 g ($p < 0.005$) and 9 g ($p < 0.001$) doses.

Globally, the MAH reported that the reduction in the number of cataplexy attacks with sodium oxybate treatment examined in trial OMC-SXB-15 was consistent with those reported previously. The MAH stated that in OMC-SXB-15 the proportion of responders was 22% with placebo and 50%, 52% and 64% with the 4.5, 6 and 9 g/d doses of sodium oxybate.

The CHMP considered that this was a relatively complex trial, given the need to washout patients from all anti-cataplectic drugs. Patients on stimulants were allowed in the study, provided they were stable during the trial. Given the different phases of trial, there has been a considerable attrition from patients screened (401) to patients randomized (285). In between, there was a single blind phase with placebo. The MAH claimed that all patients randomised and taking one dose contributed to the ITT analysis. The CHMP, however, considered that the study seemed to have methodological flaws that hampered drawing conclusions on efficacy. In particular, the clinical relevance of the effect seen was questioned in a Series of Requests for Supplementary Information (RSI). Additionally, what happened during the above-mentioned single-blind phase with placebo was not clear, in particular with regards to whether placebo responders had been selected out and to how many patients on stimulants were allowed in the trial. An analysis of placebo versus all Xyrem dosage and versus all Xyrem dosages combined, comparing the efficacy in patients using and not using stimulants concomitantly was also requested.

The MAH therefore clarified several aspects, and provided the extra analyses and data as requested. According to their clarifications and subgroup analyses, it emerged that the fraction of patients not on stimulants was 20%, and their behaviour in terms of direction and effect size was of similar magnitude to the one seen in the overall population. The re-analysis proposed by CHMP were consistent and reassuring that the effect seen is not due to bias or chance.

The primary endpoints are positive for the both doses 6 and 9 g/d but the effect size and the consistency of the secondary endpoints clearly favour the 9 g/d dose.

- **Study OMC-SXB-22**

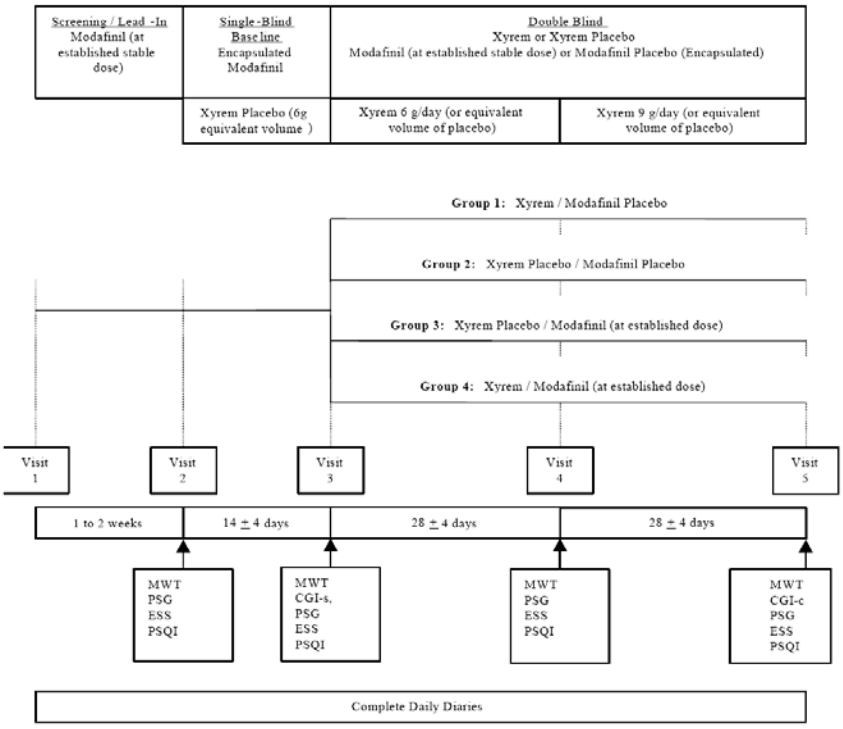
OMC-SXB-22 was a randomized, double-blind, double-dummy, placebo-controlled parallel-group comparison of sodium oxybate (6 g/d for first 4 weeks then 9 g/d for the remaining 4 weeks), modafinil, and sodium oxybate + modafinil versus placebo in 231 patients treated with double-blind treatment for 8 weeks.

Objectives

In OMC-SXB-22, patients on established stable modafinil (200 – 600 mg/d) were assessed for daytime sleepiness following the single-blind baseline period were then treated with combined single-blind modafinil and sodium oxybate placebo for 2 weeks. At the end of this period, overnight polysomnography followed by MWT established the baseline for these measures. They were then randomized to one of four treatments: sodium oxybate + modafinil; placebo + modafinil; placebo + placebo or sodium oxybate + placebo for a total treatment period of 8 weeks. Sodium oxybate was started at 6 g/d for 4 weeks and was then increased to 9 g/d (or equivalent volume of placebo). Modafinil was maintained at the established dose (or equivalent placebo). Outcome measures compared each group to the placebo group at endpoint.

In this trial, the primary measure of efficacy was excessive daytime sleepiness (EDS) as measured by objective response in MWT. Secondary measures of efficacy included EDS as measured by the ESS, change in overall severity of the patient's narcolepsy symptoms (such as number of inadvertent naps) as assessed by the investigator using the CGI-c, and effects on the PSG. The number of cataplexy attacks was not a condition of study entry nor assessed in this study.

Figure 3: Schematic of the Study Design – OMC-SXB-22



Sample size
A total of 278 patients were enrolled, and 231 were randomly assigned to treatment. The All Treated Population included 231 patients who received at least one dose of double-blind medication. The Intent-to-treat (ITT) Population included 222 patients who received at least one dose of double-blind medication and had efficacy data at baseline and Visits 4 (4 weeks) and/or Visit 5 (8 weeks). The ITT population consisted of 4 groups: placebo (55 patients), Xyrem (50 patients), modafinil (63 patients), and Xyrem plus modafinil (54 patients).

Statistical Methods
OMC-SXB-22 was analyzed in a slightly different manner to OMC-SXB-15: the change from baseline was ascertained (and tested) for each treatment, but the groups were compared with regard to the result at endpoint (rather than the change from baseline). On the other hand, as for OMC-SXB-15, samples sizes were based on the primary endpoints and significance levels were adjusted for multiple testing, as required.

Results
These results of the MWT measurements in Trial OMC-SXB-22 are summarised in table 4.

Table 4 - Summary of MWT in OMC-SXB-22

TRIAL OMC-SXB-22				
Dose Group	Baseline	Endpoint	Mean Change from Baseline	Endpoint Compared to Placebo
Placebo (n = 56)	9.9	6.9	-2.7	-
Sodium Oxybate (n=55)	11.5	11.3	0.16	**<0.001**
Modafinil (n = 63)	10.5	9.8	-0.6	**0.004**
Sodium Oxybate + Modafinil (n = 57)	10.4	12.7	2.3	**<0.001**

In trial OMC-SXB-22 (ESS = secondary endpoint), sodium oxybate at doses of 6 g/d or 9 g/d was associated with a significant reduction in ESS compared with placebo. In this trial, sodium oxybate and placebo, and sodium oxybate + modafinil each led to a reduction in ESS from baseline; in the group continuing modafinil at unchanged dose, there was no change. At endpoint, ESS was significantly lower in both sodium oxybate groups compared with placebo, but the modafinil only group did not differ significantly from placebo.

As observed in study OMC-SXB-15, in agreement with the beneficial effects of sodium oxybate shown by the ESS Scale and the MWT, sodium oxybate treatment was also associated with improvements in the number of inadvertent naps in patients (see table below).

Table 5 - Reduction in Number of Inadvertent Naps/Sleep Attacks in OMC-SXB-22

OMC-SXB-22 (median naps/attacks/week)					
	Baseline	Endpoint	Change	P-value for within-group change from baseline	P-value versus placebo for endpoint
Placebo (n = 55)	9.15	11.50	1.35	0.079	—
Sodium oxybate (n = 50)	5.63	4.00	-2.04	**0.005**	**<0.001**
Modafinil (n = 59)	10.21	9.00	-0.42	0.075	0.073
Sodium oxybate + modafinil (n = 54)	9.04	3.06	-2.85	**<0.001**	**<0.001**

With regards to Clinical Polysomnography (PSG), in OMC-SXB-22, there were statistically significant differences between the placebo group and groups treated with sodium oxybate and sodium oxybate + modafinil. Stages 3 and 4 sleep were significantly longer, average delta activity was significantly greater and non-REM sleep duration was longer in sodium oxybate-treated groups. REM sleep was significantly shorter. Sodium oxybate groups also experienced fewer awakenings per night. Treatment with modafinil alone did not result in significant changes in PSG parameters compared with placebo.

In OMC-SXB-22, sleep quality and sleep disturbance were assessed using the Patient Assessment of Sleep Quality (PSQI). Differences between the sodium oxybate and placebo groups were observed for subjective sleep quality and daytime dysfunction. There were no significant differences for other PSQI measures of sleep latency, sleep duration, habitual sleep efficiency and sleep disturbances at endpoint.

Globally, the MAH reported that, during the active treatment phase, patients who received either placebo or modafinil alone showed approximately the same degree of clinical improvement (22% responders for placebo; 19% responders for modafinil alone, not statistically significant). On the other hand, patients who received either sodium oxybate alone or sodium oxybate + modafinil showed a significant improvement over placebo-treated patients (48% responders [p =0.003] and 46% responders [p = 0.004] respectively) when assessed for change from baseline while taking stable doses of modafinil.

The CHMP considered that trial OMC-SXB-22 had some drawbacks. It has a design with 4 arms: 1) Xyrem + placebo; 2) Modafinil + placebo; 3) Xyrem + Modafinil; 4) placebo + placebo. The design of the study was such that the placebo arm was generated by patients taken out of modafinil. Thus, withdrawal from modafinil was creating an artificially deteriorated placebo group. The CHMP was interested in seeing evidence that Xyrem works over and above modafinil and whether or not they are synergic. The MAH was therefore requested to discuss the data relating to the withdrawal from modafinil, the extent to which patients deteriorated in each outcome when they were washed-out from placebo and how this would impact in the overall results. Additionally, the CHMP had reservations over that fact that MWT was a primary endpoint of the study. The MAH was therefore asked to clarify.

To address the former concern of the CHMP, in summary, the MAH explained that in Study OMC-SXB-22, the change from baseline was taken into account in determining the p-value. Results for ESS, the most reliable subjective measure of Excessive Daytime Sleepiness (EDS) in this trial, showed no worsening after withdrawal of modafinil (Visit 3) in the placebo arm compared to baseline (Visit 2). Results for MWT, the most specific and sensitive objective tool to assess EDS in this trial, followed a similar pattern from Visit 2 to Visit 3 in both median and mean changes. The MAH pointed out that, on aggregate, the data showed that Xyrem improves EDS in patients with narcolepsy using both objective and subjective measures of EDS. After treatment with modafinil was discontinued at Visit 3, daytime sleep latency decreased in the placebo group. The fact that this decrease occurred incrementally by 4 weeks at Visit 4 and then remained stable for the following 4 weeks to Visit 5 establishes this group as representing a true placebo comparison.

In contrast, all active treatment groups had significantly longer daytime sleep latency compared to the placebo group at Visits 4 and 5. In fact, both the Xyrem treatment arm and the Xyrem plus modafinil treatment arm had longer sleep latency from Visit 3 to Visit 4, while the placebo and modafinil treatment arms had a shortened sleep latency during the same period. Both the Xyrem and the Xyrem plus modafinil groups experienced further prolongation of sleep latency from Visit 4 to Visit 5, demonstrating further treatment effect with treatment time and Xyrem dose. Thus, treatment with Xyrem alone produced a daytime effect somewhat better than that seen when patients were treated with stimulants at baseline. Furthermore, the combination of Xyrem plus existing stimulant therapy produced a further prolongation of sleep latency, suggesting a synergistic or enhanced treatment benefit from the combined therapy. Additionally, the Visit 2 mean MWT in the Xyrem arm was 12.16 compared to the baseline mean MWTs of 10.13, 10.12, and 10.25 in the placebo, modafinil, and Xyrem plus modafinil groups respectively. Therefore patients in the Xyrem arm on average were

closer to normal than the other groups, making it more difficult to demonstrate a mean change from baseline in this group compared to the other treatment arms. Nevertheless the only treatment groups that showed prolongation of MWT from baseline to Visit 5 endpoint were the two arms with Xyrem active treatment.

The above-summarised data clearly indicate, in the view of the MAH, an improvement in objective measures of EDS in those patients treated with Xyrem alone or in combination with stimulants.

The CHMP considered the discussion from the MAH on this topic to be pertinent. In fact the placebo arm deteriorated from Visit 2 to Visit 5 while the other improved or stabilized. This suggests that for the MWT endpoint this trial behaved as if it was a "randomised withdrawal" trial. In fact patients previously on modafinil deteriorated without medication while the deterioration was prevented either by Xyrem or modafinil. The CHMP considered that the trial supports the claim of efficacy for Xyrem. In this sense, the trial behaved as a variant of randomized withdrawal trial. However, the results favouring the beneficial effect of Xyrem are clear.

With regards to the latter concern of the CHMP (the fact that MWT was the primary endpoint, although it does not have a functional dimension and a difference in it might not have clinical relevance) the MAH was asked to clarify. The CHMP considered that this drawback was actually balanced by the fact that the ESS as a secondary outcome, showed the same kind of effect. However, the placebo arm in the ESS and in the MWT seemed to follow a different pattern. The MAH was therefore asked to comment on the possible correlation of these 2 outcomes (MWT and ESS).

In summary, the MAH pointed out that a decrease in the ESS and an increase in the MWT are both consistent with improvement in daytime sleepiness. Results of the ESS showed a consistent trend with the MWT for all treatment arms of this study OMC-SXB-22. Similarly, an analysis was produced by the MAH that demonstrates the same statistically significant directional improvements in daytime sleepiness as measured by the number of inadvertent naps/sleep attacks per week in both the Xyrem and the Xyrem plus modafinil treatment arms. The clinical significance of this treatment effect is supported by measures of clinical global impression of change, the PSQI subjective sleep quality scores, and daytime dysfunction as measured by PSQI, all of which consistently demonstrated a clinically discernable effect.

The CHMP concurred with the explanation from the MAH that the data of all secondary outcomes are consistent and point to the same direction as the primary MWT demonstrating a benefit of Xyrem on daytime somnolence. There had indeed been deterioration in the placebo group after being washed from modafinil. The issue was that this deterioration was clearly apparent for MWT but not so much for ESS. The data presented by the MAH clarified the matter.

Conclusions on Efficacy

In addition to the data already available, the MAH provided data on two new Randomized Clinical Trials, which altogether add approximately 450 patients to the database. These trials focused in demonstrating a positive effect on daytime somnolence rather than on cataplexy, which was a secondary endpoint of the trials. The new trials had some limitations. However, globally, they demonstrated a clear effect on daytime somnolence and a consistent impact on the secondary outcomes. The other trials where daytime somnolence was a secondary objective show a consistent positive effect. The rates of responders calculated in the programme are reassuring that the effect of Xyrem on narcolepsy with cataplexy in adult patients is of clinical relevance.

The primary endpoints are positive for both doses 6 and 9 g/d but the effect size and the consistency of the secondary endpoints clearly favour the 9 g/d dose.

2.3 Clinical Safety

This submission integrates data from all completed studies up to 7 October 2005. Data from 11 clinical efficacy and safety trials are included, with data from 10 of the trials being integrated. The 10 integrated trials included a total of 781 patients treated with sodium oxybate and 260 treated with placebo.

Events that affected a higher proportion of sodium oxybate-treated patients than placebo treated patients, including all causalities and treatment-related, consisted of abdominal pain, diarrhoea, nausea, vomiting, fatigue, peripheral oedema, anorexia, dizziness, headache, abnormal dreams, confusional state, nightmare, sleep walking and enuresis. The most common adverse events associated with sodium oxybate treatment were nausea, dizziness and headache. The strongest evidence for a relationship between incidence and dose was observed for nausea, vomiting, paraesthesia, disorientation, irritability, disturbance in attention, feeling drunk, sleepwalking and enuresis. For each of these events, the incidence (both all events and treatment-related events) was notably higher after 9 g/day (and in some cases 7.5 g/d) than lower doses. Dizziness was most common at 9 and 3 g/day. The data indicate that female patients in clinical studies were more likely than male patients to experience nausea, dizziness and headache during sodium oxybate treatment. They were also more likely to experience vomiting, enuresis, diarrhoea and somnolence, although the differences between the sexes were less marked for these adverse events.

Certain adverse events were significantly more common during sodium oxybate than placebo treatment: diarrhea, nausea, vomiting, disturbance in attention, dizziness, paresthesia, tremor, enuresis, and hyperhydrosis. Overall, adverse events classed under the SOCs of gastrointestinal disorders, injury, poisoning and procedural complications, nervous system disorders, psychiatric disorders, renal and urinary disorders and skin and subcutaneous tissue disorders were significantly more common during sodium oxybate than placebo treatment. Notably, there were no additional statistically significant differences between sodium oxybate and placebo when events occurring in less than 2.0% of patients in either group were considered. For some of these more common adverse events, there could be an indication of a relationship between dose and incidence: nausea, vomiting, feeling drunk, disturbance in attention, headache, somnolence, tremor, disorientation, irritability, sleep walking, enuresis and hyperhidrosis. The incidence was higher at the highest dose. However, a high incidence of some of these events was also observed at the lowest dose used, 3 g, and so the relationship between dose and incidence is not clear-cut.

According to the MAH, overall, the additional safety data generated in the OMC-SXB-15 and OMC-SXB-22 trials had not produced any additional safety concerns. However, the CHMP had the following safety-related concerns:

1. As discussed in the Efficacy section, globally, the primary endpoints are positive for both the 6 and 9 g/d doses but the effect size and the consistency of the secondary endpoints clearly favour the 9 g/d dose. However, the CHMP considered this to be a potentially problematic dose, given the safety concerns raised at time of approval. It was noted that the proposed dose recommendations have remained unchanged from the originally approved 'cataplexy' indication, although it seems that the relevant beneficial effect on daytime somnolence appear in the high dose range. The MAH was therefore asked to comment.

The MAH, in their responses, concurred that, globally, the data do demonstrate a dose response with higher doses having an increased effect size. They pointed out that in clinical practice, clinicians typically initiate therapy at a low dose and titrate gradually (dosing recommendations call for 1.5 g increase every 1 to 2 weeks versus the increase from 6 to 9 g/night after 4 weeks in Study OMC-SXB-22) to a therapeutic dose that is both efficacious and tolerable. Since this application aimed at Xyrem being used for patients with narcolepsy with and without cataplexy, it is appropriate that the starting dose remain at 4.5 g/night. Clinicians must respond to the individual symptom pattern of each patient and the individual response and ability of each patient to tolerate a particular dose. Individual differences in tolerability also suggest that a lower starting dose is appropriate. In the clinical studies with Xyrem, roughly a third of patients

reached the 9 g/night dose, indicating that it is an effective, tolerable dose for a substantial proportion of patients. In the view of the MAH, gradual and careful titration and good clinical judgment will dictate the appropriate treatment dose for each individual patient.

The CHMP noted that the MAH could not add much to this point because dose is defined as range and patients will be titrated to response by the prescribers. The CHMP considered that future assessments of PSURs will allow the verification if patients are being pushed higher because of the daytime somnolence effect and what the consequences for the safety profile are.

2. On the grounds of the fact that the safety profile of GHB-derivate Xyrem is less favourable than for modafinil, the MAH was also requested to consider if Xyrem should only be applied in patients with narcolepsy without cataplexy as a second line treatment, for patients who are resistant to modafinil treatment.

The response given by the MAH mainly revolved around the concept that the indirect comparison of the studies available is not particularly enlightening, and argued that the two drugs are alternatives. In other words, in the MAH's view, rather than positioning Xyrem ad hoc as a second-line treatment behind modafinil, it would be more appropriate to let the prescribing physician determine the best treatment for each individual patient, taking into account that Xyrem would provide the convenience of a single medication.

Since the number of patients without cataplexy is a very small fraction and narcolepsy is a disease treated by specialized doctors the point was considered resolved, although the CHMP considered it is important to stress that the study quoted by the MAH to argue their point was designed to compare the efficacy of Xyrem to placebo (and not to modafinil), and its design does not allow for a comparison of the efficacy of modafinil versus Xyrem in patients with narcolepsy. Comparisons across trial of Xyrem versus modafinil are not straightforward, as noted by the MAH. This highlights the importance of studies for a direct comparison of the two treatment options.

3. The treatment duration of both submitted trials (OMC-SXB-15 and OMC-SXB-22) was very short, especially in relation to the chronic character of narcolepsy. These trials seem therefore insufficient to evaluate long-term safety and efficacy of Xyrem in the treatment of narcolepsy. For evaluation of maintenance of efficacy and long-term safety in narcoleptic patients without cataplexy or the new indication, additional long-term treatment data, reflecting all dose-levels, were requested by the CHMP.

The MAH's response, in summary stated that studies OMC-SXB-15 and OMC-SXB-22 support the overall safety and efficacy of Xyrem over an 8-week treatment period. However, the two Xyrem trials were conducted in a population predominantly classified as having chronic disease (lasting more than 12 months at baseline). In addition to the data from these two controlled studies, long-term safety and efficacy data are available from two previously submitted studies: OMC-SXB-21 and GHB-3.

Study GHB-3, which was submitted in the original MAA for Xyrem (March 2004), was an open-label extension trial that provides data on the safety, and secondarily on the long-term efficacy, of Xyrem over a 12-month period (mean exposure 21 months, n=117). These data demonstrate that Xyrem is well tolerated over the long term. Adverse events were consistent with those seen in controlled studies. Only a small number of adverse events were considered related to study medication at a frequency of ≤10% of the overall patient population, and these were almost exclusively mild or moderate. In addition, Xyrem produced significant long-term clinical improvement in the symptoms of narcolepsy, measured primarily by a statistically significant decrease in the frequency of cataplexy attacks. Secondary measures of clinical benefit included diminished daytime sleepiness (ESS) and reduced frequency and duration of

inadvertent naps/sleep attacks. Overall clinical benefit was evident at the earliest time point (visit 3), and was maintained at all endpoints through the 12-month study.

Study OMC-SXB-21 was a double-blind placebo-controlled study to assess the long-term efficacy of Xyrem based on the return of cataplexy symptoms on cessation of at least 6 months of open-label treatment with Xyrem (n=55). Prior to enrolling in OMC-SXB-21, patients were using Xyrem for the treatment of narcolepsy for a period of 7 to 44 months (mean – 21 months). The duration of the trial was 2 weeks. Results showed consistent maintenance of effect in Xyrem-treated patients and a statistically significant increase in cataplexy attacks in the group randomized to placebo. Further, there is a long-term safety database of 781 patients, with 334 (43%) patients treated for at least one year in doses ranging from 3 g/night to 9 g/night. Importantly, placebo patients rarely experienced adverse events associated with possible withdrawal, including anxiety, insomnia, and tremor. The conclusion was that Xyrem is effective and safe for the long-term treatment of the symptoms of narcolepsy.

The conclusion of the MAH was therefore that these data support the long-term safety and efficacy of Xyrem in patients with narcolepsy. They also provide additional information about the effectiveness of Xyrem in the treatment of both EDS and cataplexy. Taken as a whole, the data support the safety and effectiveness of Xyrem in treating the narcolepsy symptoms in several of all its aspects, offering a therapeutic benefit in treating both the nighttime and the various daytime symptoms experienced by patients with this chronic disease.

The CHMP considered that the MAH's response was acceptable. The data from the original dossier provide sufficient reassurance on the long term safety.

4. Respiratory depression.
Another safety issue that the MAH was requested to provide clarifications on was the risk of respiratory depression. The MAH provided data on respiratory parameters as requested. Xyrem may induce respiratory disturbance. This problem seems to be related in particular to the high dose 9 g/day, where 46.7% of patients had an abnormal Respiratory Disturbance Index ≥ 5. However, it is reassuring that the frequency of severe 0_2-de-saturation was not related to dose.

In conclusion, the CHMP considered that Xyrem requires careful monitoring of respiratory depression, but nothing new appears in the new dataset. The concerns are the same as those expressed during the original 'cataplexy' approval. The sentence "Xyrem has the potential to induce respiratory depression" is prominent (in bold and in a box) at the beginning of section 4.4 (Special warnings and special precautions for use) of the SPC.

Conclusions on safety
The 2 new Clinical Trials almost duplicate the placebo controlled trials safety database. The SPC has been updated in a number of events. The safety profile obtained from the current, enlarged database is consistent with what has been established before with no new concerns.

2.4. Pharmacovigilance
On the grounds that no new non-clinical or clinical safety concerns have been identified, and the proposed indication is close to the initially approved indication, the MAH proposed no updates to the existing risk management plan (originally approved at the time of the granting of the currently approved indication "treatment of cataplexy in adult patients with narcolepsy").

The CHMP did not require the MAH to submit an updated risk management plan because the safety profile of Xyrem was not considered to be different for the new indication.

3. CHANGES TO THE PRODUCT INFORMATION

As a result of the various requests for supplementary information described above, their provision and assessment, the CHMP considered that all clinical issues had been addressed to satisfaction by the

MAH. On the other hand, the wording of the indications statement initially submitted by the MAH with this application (changing "*Treatment of cataplexy in adult patients with narcolepsy*" to "*Treatment of narcolepsy in adult patients*") was considered not to reflect adequately the scientific findings emerging from the re-analyses carried out by the MAH in their responses to the RSIs.

The CHMP considered that the therapeutic indications statement should read "***Treatment of narcolepsy with cataplexy in adult patients***".

In addition, the CHMP considered that other sections of the SPC (namely, section 5.1) required extensive modifications, to reflect appropriately the outcome of the clinical studies supporting the application.

Additionally, section 5.1 of the SPC required extensive revision, according to the following points:

- the MAH was requested to specify the primary endpoints (CGI-c; ESS; MWT and number of cataplexy attacks) and present the results of the primary analysis individually for each of the studies;

- the number of patients included in the analysis of the primary endpoints should be corrected;

- overall, less emphasis should be put on the secondary endpoints;

- a statistical comparison of modafinil/Xyrem versus Xyrem/placebo and modafinil/Xyrem versus modafinil/placebo has not been presented. In addition, these comparisons were not specified as outcome of the study. Therefore the MAH should delete the sentence:
  "*Trial 2 demonstrated that when patients are maintained on a stable dose of modafinil, patients taking both sodium oxybate and modafinil showed additional improvement over sodium oxybate or modafinil alone in these three measures of daytime sleepiness.*"

The MAH agreed with the requests from the CHMP, and provided Product Information amended accordingly.

4. OVERALL CONCLUSIONS AND BENEFIT/RISK ASSESSMENT

The data provided and their re-analyses carried out at the request of the CHMP were positive and consistent, and have shown a clinical relevant effect on daytime somnolence of narcoleptic patients, particularly in doses of 6 to 9gr/d. The MAH also provided satisfactory answers to the safety concerns raised by the CHMP during this procedure.

Based on the CHMP review of data on safety and efficacy the CHMP considered that the risk-benefit balance of Xyrem in the treatment of narcolepsy with cataplexy in adult patients was favourable.

5. CONCLUSION

On 24 January 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.