

NDA 21196
Xyrem® for Narcolepsy
Orphan Medical, Inc.

Comments About Sleepwalking

Background

In this NDA and especially in the Scharf Study, the term “sleepwalking” has been used as a verbatim (investigator) term for a common adverse event. The COSTART preferred term under which this entity has been coded is “sleep disorder.”

The sponsor has not discussed this adverse event, either in the original NDA submission or in this Amendment. Given the frequency and potential/actual consequences of this adverse event (see below) I have chosen to discuss it further briefly

In most instances of “sleepwalking” in this NDA, a detailed description of patient behavior during that adverse event is not available.

The medical term “sleepwalking” refers to a non-REM parasomnia classified as an arousal disorder. During episodes patients exhibit complex behaviors including automatic and semi-purposeful motor activities: sitting up in bed, walking, climbing stairs, opening and closing windows and even more complex tasks, such as preparing food, may be features. Acts that are destructive or harmful may be seen, such as throwing objects, and climbing out through a window. During and immediately following episodes patients are confused; they have amnesia for the episodes. It is not at all clear that the term “sleepwalking” has a similar connotation when used in this NDA, or that it refers to a single clinical entity. In the majority of instances of sleepwalking in the Scharf study, this term appears to be derived from daily logs maintained by patients

There does not appear to be an association between narcolepsy and typical sleepwalking as defined in the paragraph above. However about 50% of narcoleptic patients have periods of automatic behavior that are described as memory lapses or blackouts; patients have amnesia for their activities during these episodes. Semi-purposeful activity is possible during such episodes which may manifest with phenomena such as walking into objects, getting lost while driving, and writing unintelligibly. Such episodes are believed to be due to micro-sleeps that intrude into wakefulness, and are most frequent in the mornings. Again there is no information supplied with the NDA that would strongly suggest

that any of the “sleepwalking” episodes correspond to automatic behavior occurring as part of narcolepsy.

Incidence Of “Sleepwalking” In Xyrem® NDA

Controlled Clinical Trial OMC-GHB-2

The incidence of adverse events coded under the COSTART preferred term “sleep disorder” is as follows among the 4 treatment groups

Dose Group	Total Number Randomized	Number of Patients with “Sleep Disorder” (COSTART)	% of Patients with “Sleep Disorder” (COSTART)
Placebo	34	1	2.9
3 g/day	34	2	5.9
6 g/day	33	4	12.1
9 g/day	35	5	14.3

The sponsor has attempted to characterize the term “sleep disorder” further in the following table which I have copied from the OMC-GHB-2 clinical trial report

Description	Placebo	GHB		
		3g	6g	9g
Prolonged sleep paralysis	1	1	2	5
Sleep walking	0	0	0	2
Poor sleep maintenance/ frequent arousal	0	1	2	1
Microsleep	0	0	1	0

Integrated Clinical Trials (of which OMC-GHB-2 is a component)

“Sleep disorder” (COSTART) occurred in 46/402 (11.4%) of patients participating in these trials. There was no dose-response seen and the sponsor has not characterized this adverse event further except in the case of those participating in OMC-GHB-2. Thus it is unclear how many patients recorded as having a “sleep disorder” (COSTART) might have been considered to have “sleepwalking”

Scharf Trial

Based on my review of all the Case Report Forms for this study, 45/143 (31.5%) of patients were listed as having one or more episodes of “sleepwalking.” A single patient (# 01-042, initials MJM) is described as having 346 episodes, and many patients had multiple episodes.

The patients listed as having “sleepwalking” constitute the entire cohort of those coded under the COSTART preferred term “sleep disorder” in this study

Characterization Of “Sleepwalking” Episodes

As already indicated the sponsor has not provided more detailed descriptions of patient behavior during these episodes except in a very small number of instances.

I have not attempted to characterize the “sleepwalking” episodes in regard to patient demographics, duration, severity and seriousness of episodes, GHB dose at onset, concomitant medications and illnesses, outcome and other parameters. I currently lack both the time and resources to perform such an analysis. The sponsor should, however, be required to perform such an analysis prior to approval. Such episodes, regardless of their etiology, have had serious consequences as outlined below.

Consequences Of “Sleepwalking” In Xyrem® NDA

Narratives are provided below for patients who were reported to have events of serious or potentially serious consequence during episodes of “sleepwalking.” These consequences include taking an overdose of GHB as well as other actions. Several of these narratives are elsewhere in this review but are reproduced here for convenience. All instances occurred in the Scharf study.

Patient 01-215 (Initials AEB)

This 46 year old woman with narcolepsy, who sustained a skull fracture 5 years prior to study entry, took GHB in a variable dose of 4.5 to 10.5 g/day in 2 or 3 divided doses despite being prescribed 7.5 g/day (this is not consistent with what has been entered in the medication logs in the Case Report Form. About 4 months after entering the study she reported symptoms of nausea, a tipsy feeling, blurred vision, and a swollen face and hands. These symptoms persisted for 14 days, no action was taken, and her doses subsequently were variable and as high as 10.5 g/day. She continued in the study for a further 4 years when she was discontinued on account of non-compliance which involved not submitting daily sleep log diaries and modifying dosing schedules without prior consultation with Dr Scharf.

A number of unexplained fits of laughter (termed “hysterical” in one instance, and “uncontrollable” at other times), and **episodes of “sleepwalking” (during one of which she tried to drink nail polish remover)**. Episodes of headache, nausea, dizziness, blurred vision, enuresis, “fogginess”, “stumbling around-unsure of self on feet after gamma”, “drugged effect, vision blurred, unsteady on feet”, “drunken stupor; rage”, other similar events, and sleeplessness, were also noted during the study.

A telephone contact with the patient 12 ½ years after she discontinued from the study indicated that her neurological adverse events, with the exception of blurred vision, had resolved once GHB was discontinued.

Patient 01-017 (Initials WF)

This 63 year old man had a history of narcolepsy and sleep apnea. as well as hypertension. Initial physical examination is reported to have shown a “mild-to-moderate degree of oropharyngeal compromise.”

He began taking GHB in a dose of 4.5 g daily. **About 11 months after enrolling, in an incident attributed to possible sleepwalking he ingested an additional estimated 9 g of GHB in addition to his first nightly 3 g dose of the drug. He drove himself to an emergency room, where he was administered ipecac and slept for 2 hours**

Approximately 1 ½ years after enrolling in the study he was hospitalized after an overdose of GHB 18 g, again attributed to sleepwalking. At the time of hospitalization he was comatose and unresponsive. He needed intubation and artificial ventilation, and awoke 6 hours later. He continued in the study.

Other significant items of information regarding this patient are as follows

- He had many episodes of sleep walking and multiple episodes of urinary incontinence.
- In 2 instances episodes of sleep walking and urinary incontinence are listed in the Case Report Form as occurring on the same day although there is no evidence presented that they occurred at the same time.
- On the days when both incontinence and sleep walking are listed as having occurred, the patient's prescribed dose was 7.5 g/day
- As noted above this had multiple episodes of sleep walking that did not occur on the same days as his episodes of incontinence.
- He also reported muscle jerks over the front of his trunk over a period of several years while taking GHB. These were stated to be most prominent when lying in bed in the morning as the last dose of GHB was wearing off; they could be controlled voluntarily and would disappear with ambulation, returning when at rest.
- He developed congestive heart failure during the study and died about 5 years after study entry. While participating in the study he underwent a thoracotomy for a right lung nodule that was confirmed to be a squamous cell carcinoma.

Patient 01-267 (Initials RMM)

This 65 year old woman had a history of obesity, sleep apnea on treatment, and narcolepsy. She began taking GHB in a dose of 4.5 g daily.

About 4 ½ years after study entry she was reported to have taken an overdose of GHB, consuming a third nightly dose instead of merely two doses. The patient's daughter reported that the patient was shortly afterward incontinent of urine, awoke and (for unclear reasons) was covered with spaghetti sauce. She also appeared dazed and confused. Her diaries are unavailable for that period and it is therefore unclear what her regular dose of GHB was at the time. She was taken to an emergency room but had recovered by that time. She was reported to have continued GHB after that episode but ceased returning any daily diaries at all beginning about 5 ¼ years after study entry and was therefore recorded as having left the study on account of non-compliance. Repeated letters to the patient from the study center were reportedly unanswered. Further information about this patient is unavailable.

During her participation in the study she was also recorded to have multiple episodes of sleepwalking and multiple additional episodes of urinary incontinence, not apparently occurring contemporaneously. She was also seen at an emergency room for an episode of somnolence which was felt to be related to her sleep apnea. She reported swollen ankles and wrists, and pain, numbness and tingling in her feet.

(It is not clear from the above or from the Case Report Form whether the overdose occurred during an episode that would have been considered to represent "sleepwalking")

Patient 01-206 (Initials DRS)

This 62 year old woman had a history of narcolepsy, hypertension and heavy smoking. She began taking GHB in a dose of 3 g/day.

While participating in the trial she had 7 episodes of sleep walking. 2 episodes which occurred, separated by a 2-day interval, 7 ½ months after she entered the study, led to her discontinuing GHB. During each of these episodes she was found by her husband with a burning cigar or cigarette in her hand, apparently not aware of having been smoking. On one of these occasions she was found

in a room other than their bedroom asleep with a cigar in her hand. On the second occasion the cigarette was found to be burning her nightgown; her husband threatened at that point to leave her unless she stopped taking GHB. The patient's entries in her daily sleep log indicate that she was unaware of her actions during these episodes and had no personal recollection of them subsequently .

Reviewer's Comments

- In the absence of adequate clinical descriptions in most instances it is unclear what the adverse event investigator term "sleepwalking" represents, or whether it refers to single or multiple entities.
- Regardless of what the term "sleepwalking" means in the context of this NDA, it is clear that such episodes are common; almost one-third of patients participating in the long-term Scharf safety study did have one or more such occurrences, and a single patient is recorded as having as many as 346 episodes. The incidence of this adverse event in the entire Integrated Clinical Trials grouping is unknown (except for a single study, OMC-GHB-2)
- The few clinical descriptions of this adverse event that are available in this NDA suggest that during "sleepwalking" episodes patients may be confused and may act in a manner that could be prejudicial to their own safety and that of others.
- The sponsor has not, so far, attempted to analyze this adverse event as an entity
- The fairly high incidence and potential consequences of such episodes make it essential that the sponsor should be asked to better characterize the instances of sleepwalking in this NDA prior to the drug being approved for marketing.
- In this reviewer's opinion (and on a largely speculative basis) it is possible that the term "sleepwalking" as used in this entity could be describing one or more of the following entities
 - An acute confusional state induced by GHB
 - Automatic behavior of narcolepsy
 - Partial complex seizures (these are unlikely to be caused by GHB)
 - An arousal disorder akin to true sleepwalking