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(Article begins on next page)

Long-Term Compliance, Safety, and Tolerability of Sodium Oxybate Treatment in Patients with Narcolepsy Type 1: A Post-Authorization, Non-Interventional Surveillance Study

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Abstract

Study Objectives

To evaluate adherence to sodium oxybate prescribing information for indication and dosage, patients' compliance with instructions for use, safety/tolerability in routine clinical practice, and abuse potential.

Methods

A post-authorization, non-interventional surveillance study (NCT00244465) in patients who were prescribed sodium oxybate according to current practice by sleep disorders specialists. Patients were monitored for ≤18 months.

Results

Overall, 749 patients were enrolled; 730 included in the intent-to-treat population (narcolepsy type 1 n=670, other indications n=60). We report on patients with narcolepsy type 1 (female 47.9%, mean age 39.4 y); 495/670 (73.9%) completed the study. Median dose: at start of study 4.5 g/night, 6 g/night throughout study, in two equal doses. According to the treatment compliance checklist, 35.5% of patients consumed alcohol, 19.3% took the medication <2 h after food, and 27.1% did not adhere to recommended time schedule, with few associated treatment-emergent adverse events (TEAEs). Incidences of higher-than-recommended doses, difficulty in preparing doses, and abuse were low. TEAEs were reported by 67.3%, most frequently headache (11.6%) and nasopharyngitis (6.4%). Discontinuation due to TEAEs: 8.8%. Serious TEAEs: 6.4%. There were no reports of respiratory depression. No particular safety concerns were identified in pediatric or elderly patients, or those with underlying sleep apnea.

Conclusions

In this large post-authorization safety study of sodium oxybate use, indication and dosage prescribing recommendations were generally followed, and most patients complied with instructions, with deviations around alcohol consumption, eating before dosing and timing. The overall safety profile was consistent with previous observations; incidence of abuse was low.

Section: Neurological disorders

Keywords: Sodium oxybate; Narcolepsy; Narcolepsy – pharmacotherapy; Pediatrics – narcolepsy; Post-authorization study; Compliance

Clinical trial: Post-authorization, non-interventional, surveillance, pharmacoepidemiology study to evaluate long-term safety, tolerability and compliance in administration of Xyrem® (sodium oxybate) oral solution in patients who receive treatment with this medication in regular clinical practice. https://clinicaltrials.gov/ct2/show/NCT00244465, ClinicalTrials.gov: NCT00244465

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Statement of significance

Sodium oxybate is an effective drug for reducing cataplexy attacks and excessive daytime sleepiness in patients with narcolepsy. Administration of sodium oxybate presents some practical challenges, including dose titration, twice nightly administration, and need for abstinence from alcohol. This was the largest post-authorization, non-interventional surveillance study of patients with narcolepsy conducted to date. It provides important long-term, real-world data on the use of sodium oxybate in clinical practice across Europe. Prescribing recommendations were generally followed, and most patients complied with instructions. No new safety concerns were identified. The incidence of abuse was low.

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Introduction

Narcolepsy has been subdivided into type 1 and type 2.[1] Excessive daytime sleepiness and cataplexy are core features of narcolepsy type 1, while cataplexy is absent in narcolepsy type 2. Diagnosis may be confirmed by sleep laboratory testing using polysomnography and the multiple sleep latency test. Measurement of hyprocretin-1 in the cerebrospinal fluid (CSF-hrct-1) can also differentiate narcolepsy type 1 (CSR-hrct-1 deficient) from narcolepsy type 2 (CSF-hrct-1 normal or undocumented).[1] However, in 24% of patients with type 2 narcolepsy, low levels of hypocretin-1 are seen, and in 8%, intermediate levels are seen, between 110 and 200 pg/mL.[2]

Sodium oxybate[3] is the sodium salt of the inhibitory neurotransmitter, gamma-hydroxybutyrate (GHB).[4] Sodium oxybate is approved in Europe to treat adults with narcolepsy with cataplexy. In double-blind, placebo-controlled studies, sodium oxybate significantly reduced narcolepsy symptoms including the frequency of cataplexy attacks[5,6] and excessive daytime sleepiness.[7] A further double-blind, placebo-controlled study showed that sodium oxybate was effective for the treatment of excessive daytime sleepiness both as monotherapy and in combination with modafinil.[8] Sodium oxybate was well tolerated both in short-term studies[5,7,8] and in a long-term, open-label extension study.[9] The most commonly reported adverse events (AEs) in clinical trials were dizziness, nausea, and headache.[10] However, sodium oxybate is a potent central nervous system (CNS) depressant, and has the potential to induce respiratory depression. Other serious AEs reported infrequently in clinical trials include suicide attempt, psychosis, and convulsions. Moreover, illicit formulations of GHB have been used for abuse.[11] Due to the risk of serious AEs and abuse, sodium oxybate is a controlled drug requiring a special prescription in Europe, and is prescribed through a restricted availability program in the USA.

The recommended starting dose of sodium oxybate is 4.5 g/night (twice 2.25 g), titrated according to efficacy and tolerability to a maximum of 9 g/night (twice 4.5 g). Sodium oxybate is absorbed and eliminated rapidly with a short half-life of around 40 min.[12] Consequently, to allow a full night's sleep, patients are instructed to take two equal doses each night – one at bedtime and the second 2.5–4 h later. Both doses should be taken while in bed as sodium oxybate can cause rapid sleep onset. The medication is provided in liquid form to be measured out using a graduated syringe into a separate child-resistant container for each dose, and then diluted with water. Patients are advised to take the medication at least 2 h after food and not to consume alcohol during treatment. Sodium oxybate is contraindicated in patients with hypersensitivity to any of the ingredients, major depression, succinic semialdehyde dehydrogenase deficiency, or those taking opioids or barbiturates.

A post-authorization, non-interventional surveillance study was conducted at the request of the European Medicines Agency (EMA) to inform the risk management plan for sodium oxybate. The EMA's main areas of concern were the narrow safety margin of sodium oxybate, in particular the risk of respiratory depression, and the potential for abuse or misuse. The objectives of this study were to evaluate adherence to the prescribing information, patients' compliance with instructions for use, AEs occurring in patients being treated with sodium oxybate in routine clinical practice, and broadening the knowledge about the potential for misuse, overdose, and abuse.

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Methods

Study design

This post-authorization, non-interventional surveillance study (C00302, NCT00244465) was conducted between May 2006 and September 2016 in 41 centers in Europe. The study enrolled any patients, irrespective of diagnosis, who had been prescribed sodium oxybate by a physician specializing in sleep disorders, and who were willing for their data to be collected. The regulatory authorities in Switzerland only requested the following exclusion criteria: age <18 y, allergy to any ingredient of sodium oxybate, succinic semialdehyde dehydrogenase deficiency, current opioid or barbiturate treatment, pregnancy, or breastfeeding. Sodium oxybate was prescribed according to current practice, with no recommendations or restrictions apart from those described in the marketing authorization. Patients were monitored according to normal good clinical practice for a target duration of 18 months. Study visits or telephone monitoring were conducted at weeks 0, 2, 4, and 12, and then at 3-monthly intervals up to week 72. Visits could be replaced by a telephone call at weeks 4, 24, 36 and 60. A follow-up visit was scheduled 2 weeks after the last dose of sodium oxybate. Vitals signs were measured at weeks 0, 2, 4, 12, 48, 72, and at the follow up visit.

This study was conducted in accordance with the Guideline for Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005), the Declaration of Helsinki (World Medical Association 2013), and local laws and regulations. The study protocol was approved by institutional review boards at all study sites, and written informed consent was obtained from all patients or their legal representatives before enrollment.

Assessments

Information about the prescribed dose and manner of sodium oxybate administration was collected at each patient visit. A treatment compliance checklist was completed by the physician at each study visit to collect information related to misuse, overconsumption, abuse and inappropriate use, and any resulting AEs. Safety and tolerability assessments were AEs, blood pressure, heart rate, and body mass index (BMI). Serious AEs were defined as AEs that, at any dose, were life-threatening, a birth defect, required in-patient hospitalization, resulted in persistent or significant disability, or death, or were judged to require medical or surgical intervention to prevent one of these outcomes. AEs of special interest were defined as those related to respiratory depression, hypoventilation or apnea, convulsions, psychiatric disorders, sleepwalking, urinary incontinence, changes in body weight, endocrine disorders, or electrolyte abnormalities. No assessments to objectively monitor changes in underlying sleep apnea were planned.

Statistical analysis

The sample size calculation was based on guidance provided by the EMA. For a planned sample size of 750 patients and an overall AE incidence rate of 50%, the two-sided 95% confidence interval had an accuracy of ± 3.6%.

The intent-to-treat (ITT) population was defined as all patients who were enrolled and received at least one dose of sodium oxybate. Patients were censored at the date of the last

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available information. If data for any patient were collected for longer than 18 months, a cut-off date of 18 months + 30 days was applied. Treatment persistence was analyzed using Kaplan-Meier methodology. No formal statistical testing was performed.

This report focuses on patients with the indication narcolepsy type 1. With a lower number of patients in the ITT population with narcolepsy type 1 (n = 670) compared with the planned sample size (n = 750), accuracy of the confidence interval changed from ± 3.6% to ± 3.8%, which was considered acceptable for this type of study. Treatment-emergent adverse events (TEAEs) were summarized for all patients with narcolepsy type 1, and for subgroups defined by age (<18, >65 y), and history of underlying sleep apnea. Demographic, median dose, exposure, compliance, and TEAE data for patients with indications other than narcolepsy type 1 are provided in the Supplemental Material.

Results

Participants

A total of 749 patients were enrolled, and 730 were included in the ITT population. In the ITT population, 329 (45.1%) patients were already on sodium oxybate at study entry and 401 (54.9%) initiated treatment at study entry. Sodium oxybate was prescribed to treat narcolepsy type 1 for 670 patients. The remaining 60 patients had other, potentially off-label indications, most commonly narcolepsy unspecified (n = 24), narcolepsy without cataplexy (n = 23) and idiopathic hypersomnia (n = 11). The patients with narcolepsy type 1 were recruited in Spain (n = 272), Germany (n = 128), Italy (n = 97), Belgium (n = 59), United Kingdom (n = 49), Switzerland (n = 33), Austria (n = 16), Czech Republic (n = 11), and Ireland (n = 5). The patients with indications other than narcolepsy type 1 were mostly recruited in Spain (n = 27) and Germany (n = 26), as well as Italy (n = 4), Ireland (n = 2), and Switzerland (n = 1).

Patient disposition is shown in Figure 1. Of the 670 patients with narcolepsy type 1, 495 (73.9%) completed the study. The most common reasons for discontinuation were AEs (9.7%) and loss to follow up (6.9%).

For the patients with narcolepsy type 1, mean (standard deviation [SD]) age at baseline was 39.4 (16.5) y, with 54 (8.1%) and 57 (8.5%) patients aged <18 and >65 y, respectively. Approximately half the population were female (321, 47.9%). Mean (SD) BMI was 28.3 (5.7) kg/m^2. Median dose of sodium oxybate was 4.5 g/night (IQR 4.0 g/night, range 0.0–13.5 g/night) at the start of the study, increasing to 6 g/night (IQR 3.0 g/night, range 0.0–9.5 g/night) from week 2 up to month 1; the median dose was 6 g/night (IQR 3.0 g/night, range 0.5–10.5 g/night) throughout the whole study. Median (range) duration of exposure was 507 (1–577) days. Demographic characteristics, median dose, and duration of exposure for the patients with indications other than narcolepsy type 1 are shown in Table S1.

Treatment persistence is shown in Figure 2 (narcolepsy type 1) and Figure S1 (other indications). For patients with narcolepsy type 1, the Kaplan–Meier estimated probability of treatment persistence at week 78 was 0.71. Total exposure to sodium oxybate was 795.92 patient-years.

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Compliance, and abuse potential

For patients with narcolepsy type 1, responses on the treatment compliance checklist are reported below and in Table 1. Responses are summarized for patients with indications other than narcolepsy type 1 in Table S2.

Sodium oxybate was taken within 2 h of food consumption by 19.3% of patients overall; daily (29, 4.3%), on a few days per week (41, 6.1%), or on a few days per month or less (58, 8.7%). Around one quarter of patients (27.1%) did not take sodium oxybate according to the recommended time schedule, at a frequency of daily (48, 7.2%), a few days per week (43, 6.4%), or a few days per month or less (89, 13.3%). Consumption of alcohol was common (35.5% of patients) but was mostly limited to a few days per month or less (176, 26.4%), with few patients drinking alcohol daily (23, 3.4%) or on a few days each week (37, 5.5%). Only a few patients took sodium oxybate at a dose or frequency higher than recommended (<4% each). During the study, the mean (SD) number of days with a dose of >9 g/night was 2.0 (24.1) per patient, ranging from 0 to 460 days. Eight patients (1.2%) had difficulty in preparing doses. Incidents related to abuse potential were rare (premature refill requests, inappropriate dose adjustment requests, continued use after drug termination, sodium oxybate use by other household members).

TEAEs associated with treatment compliance checklist items were uncommon (Table 1). There were three cases of serious TEAEs that were considered associated with misuse or abuse. One 18-year-old woman had difficulty in preparing the dose resulting in an inappropriate schedule of drug administration (accidental overdose). She took a second dose of sodium oxybate immediately after the first dose, resulting in sleepiness. She was observed in hospital overnight and fully recovered. A 12-year-old girl had serious upper abdominal pain which was considered to be associated with a premature request for prescription refill. In the third case, the girlfriend of a 36-year-old male patient ingested an unknown dose of sodium oxybate with alcohol on one occasion (intentional drug misuse). No clinical symptoms were reported.

Adverse events

For patients with narcolepsy type 1, TEAEs are reported below and are summarized in Table 2. TEAEs are summarized for patients with indications other than narcolepsy type 1 in Table S3.

At least one TEAE was reported by 67.3% (451/670) patients; the most frequently reported (incidence ≥5%) were headache, nasopharyngitis, decreased weight, dizziness, and nausea. Of 434 patients who had an increase in dose of sodium oxybate during the study, 47 (10.8%) and 103 (23.7%) reported a TEAE within 1 day or 1 week, respectively. Of 299 patients with a decrease in dose, 37 (12.4%) and 57 (19.1%) reported a TEAE within 1 day or 1 week, respectively. Sodium oxybate was discontinued permanently due to TEAEs in 59/670 patients (8.8%). The TEAEs that most frequently resulted in discontinuation (≥0.5%) were nausea (eight patients, 1.2%), depressed mood, depression, and dizziness (four patients, 0.6% each). All TEAEs leading to permanent discontinuation of sodium oxybate are given in Table S4. All severe TEAEs are supplied in Table S5.

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Serious TEAEs were reported by 43/670 (6.4%) patients. The most frequent were depression (three patients, 0.4%), angina pectoris, inguinal hernia, and suicide attempt (two patients, 0.3% each). All serious TEAEs are given in Table S6. One death was reported during the study in a 59-year-old male with no recorded medical history apart from narcolepsy with cataplexy; concomitant medication included clomipramine, dexamphetamine, and furosemide. Sodium oxybate was discontinued due to a TEAE of severe dyspnea. The patient died due to cardiac failure approximately 3 months after discontinuation. The dyspnea and cardiac failure were not considered by the investigator to be related to study drug.

At least one TEAE of special interest was reported by 28.1% of patients (Table 3). There were no reports of respiratory depression, and the incidence of dyspnea was 0.7%. Convulsions were reported in five patients (preferred terms: epilepsy, 2 patients; myoclonus, 2 patients; seizure 1 patient), of whom one had a history of epilepsy. The TEAEs in the four patients without a history of epilepsy were reported by the investigator as epileptic seizure, convulsions (probably dissociative episode), facial myoclonus, and myoclonus. The most frequent psychiatric disorders were depression (29 patients, 4.3%) and confusional state (10 patients, 1.5%). Of the 40 patients reporting TEAEs related to depression (depression, 29 patients, 4.3%; depressed mood, 9 patients, 1.3%; suicidal depression, 1 patient, 0.1%; and adjustment disorder with mixed anxiety and depressed mood, 1 patient, 0.1%), 11 patients (27.5%) had a medical history of depression, and 3 patients (7.5%) had a medical history of depressed mood. Somnambulism occurred in 21 patients (3.1%). TEAEs related to urinary incontinence included enuresis (18 patients, 2.7%), urinary incontinence (16 patients, 2.4%), and nocturia (five patients, 0.7%). Decreased and increased body weight were reported by 35 (5.2%) and four (0.6%) patients, respectively. Hypothyroidism occurred in three patients (0.4%). No electrolyte abnormalities were reported as TEAEs.

There were two suicide attempts (0.3%) during the study; in both cases, sodium oxybate was discontinued and the patient recovered. In the first case, a 16-year-old male adolescent took 9.5 g of sodium oxybate as an overdose. He had a depressed mood considered to be due to a reluctance to accept his narcolepsy diagnosis, but no previous history of suicide ideation or attempts. Concomitant medication included methylphenidate. The investigator considered it highly probable that the suicide attempt was related to study drug. The other suicide attempt in a 44-year-old woman did not involve an overdose of sodium oxybate, but was considered by the investigator to be probably related to study drug. Suicidal depression was reported in one patient (0.1%); a 52-year-old man with a history of hypertension, and no history of depression. The investigator considered it highly probable that this TEAE was related to study drug, and symptoms resolved after reduction of the dose. An additional two patients took overdoses of sodium oxybate without recorded suicidal intent; in both cases the investigator considered it highly probable that the overdose was related to study drug. A 61-year-old man with a history of insomnia, type 2 diabetes, and hypercholesterolemia took 9 g as a single dose because he had to wake up early the following morning. Concomitant medication included fluoxetine and modafinil. He subsequently woke up with intense dizziness and confusion which resolved spontaneously; sodium oxybate treatment was continued. A 34-year-old woman with a history of amenorrhea, and taking fluoxetine and methylphenidate concomitantly, took an overdose of 6 g and recovered; sodium oxybate was discontinued.

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Six patients became pregnant while receiving treatment with sodium oxybate; all discontinued treatment. Five patients delivered healthy babies, one was lost to follow up. Two patients developed gestational diabetes.

Adverse events in children and elderly patients

There were 54 patients with narcolepsy type 1 who were aged <18 y (range 6–17 y) at study entry. The median dose of sodium oxybate in this subgroup was 3.5 g/night (IQR 4.2 g/night; range 0.0–9.0 g/night) at the start of the study and 5.4 g/night (IQR 2.5 g/night; range 0.5–10.5 g/night) across the entire study duration, with a total of 67.61 patient-years of drug exposure. TEAEs were reported by 36 (66.7%) patients, most commonly headache, enuresis, and nasopharyngitis (Table 4).

Fifty-seven patients were enrolled who had narcolepsy type 1 and who were aged >65 y (range 66–79 y) at study entry. The median dose of sodium oxybate in this subgroup was 6.0 g/night (IQR 2.5 g/night; range 1.6–9.0 g/night) at the start of the study and 6.0 g/night (IQR 2.55 g/night; range 2.5–9.0 g/night) across the entire study duration, with a total of 66.09 patient-years of drug exposure. TEAEs were reported by 42 (73.7%) patients, most commonly dizziness, decreased weight and nausea (Table 4).

Adverse events in patients with sleep apnea

TEAEs were reported by 61/87 patients (70.1%) with narcolepsy type 1 and a history of underlying sleep apnea, most frequently headache and nasopharyngitis (Table 5).

Vital signs and physical examinations

There were no clinically significant changes in blood pressure, heart rate and BMI during the observation period.

Discussion

This is the largest post-authorization study that has been conducted to date in patients with narcolepsy. A total of 730 patients were treated and included in the intent-to-treat population, including 670 patients with a diagnosis of narcolepsy type 1, who received sodium oxybate at a median starting dose of 4.5 g/night and 6 g/night across the whole study. Study completion rate was high, with 73.9% of patients with narcolepsy type 1 and 61.7% with other, potential off-label, indications (mostly narcolepsy unspecified or narcolepsy type 2) completing 18 months of treatment. This report focuses on results for the subgroup of patients with narcolepsy type 1, and reports on almost 800 patient-years of drug exposure.

One of the objectives of this study was to determine whether prescribing recommendations and instructions for use of sodium oxybate are followed in a real-world setting. Data collected suggested that prescribing recommendations regarding indication and dosage were generally followed. The majority of patients (670/730) were prescribed sodium oxybate to treat narcolepsy type 1. The median starting dose and median dose throughout the whole study was consistent with the recommended dose range of sodium oxybate. Although some flexibility with dose is required in clinical practice, few patients actually took doses >9 g/night. Treatment with sodium oxybate presents a number of practical challenges for the patient with regard to timing and preparation of doses. A substantial proportion of patients indicated

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by their responses on the treatment compliance checklist that they did not always adhere to instructions concerning the dose schedule (27.1%) or taking the medication at least 2 h after food (19.3%). Consumption of alcohol was seen in a high proportion of patients (35.5%), although most stated that this only occurred on a few days per month or less and resulted in few clinically significant symptoms. Misuse of sodium oxybate was rare and was associated with few AEs, suggesting that this was not likely to have negative consequences. Despite the requirement for making up two separate doses per night, almost all patients (98.8%) stated that they experienced no difficulty in preparing their medication.

TEAEs were reported by around two-thirds of patients (67.3%) with narcolepsy type 1, most frequently (incidence ≥5%) headache, nasopharyngitis, decreased weight, dizziness, and nausea. There was no evidence that TEAEs were related to either an increase or decrease in dose. Direct comparisons of post-authorization study data with clinical trial data are limited since real-world studies enroll a broader population with regard to diagnosis, medical history, and other characteristics, and there are also differences in study design such as the lack of a placebo group. Nevertheless, the safety profile of sodium oxybate observed in this study was in line with previous reports. Across the clinical development program, the most commonly reported AEs (10–20%) with sodium oxybate were dizziness, nausea, and headache.[10] Pooled data from placebo-controlled clinical trials in patients with narcolepsy (sodium oxybate 3–9 g/night, n = 398; placebo, n = 213) showed that the most common TEAEs (incidence ≥5% and at least twice that of placebo) were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.[3] A meta-analysis of six randomized controlled trials reported that patients who received sodium oxybate had a statistically greater incidence of TEAEs than placebo, particularly nausea, vomiting, and dizziness.[13] Weight loss was common in clinical trials, reported by up to 10% of patients,[10] consistent with the incidence of 5.2% seen in this post-authorization study. Cumulative post-marketing and clinical safety experience with sodium oxybate over the first 6 y post-launch has been reviewed.[14,15] Both a formal Post-Marketing Evaluation Program and spontaneous post-marketing AE reporting demonstrated lower AE incidences than those observed in the clinical trials. No new safety concerns were identified in either this post-authorization study or previous post-marketing experience.[14]

Sodium oxybate is a CNS depressant with the potential to induce respiratory depression, special caution is thus advised when it is prescribed for patients with underlying respiratory disorders.[10] A study in patients with obstructive sleep apnea has indicated that sodium oxybate at a dose of 9 g/night may be associated with central apnea and oxygen desaturation in some patients,[16] although short-term use of a lower dose did not have respiratory depressant effects.[17] Clinically significant respiratory depression has been reported in patients with narcolepsy who were treated with sodium oxybate in clinical trials.[3] In contrast to the studies conducted during the clinical development of sodium oxybate, this post-authorization study did not exclude patients with sleep-disordered breathing. However, there were no reports of respiratory depression, and dyspnea was uncommon (0.7%). Patients with underlying sleep apnea had a similar safety profile to the overall population.

Use of sodium oxybate is not recommended in patients with epilepsy, since seizures have been observed in patients treated with this medication.[10] Convulsions were uncommon in this study – five patients (0.7%) reported some type of convulsion during treatment. One of these patients had a previous history of epilepsy.

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Psychiatric AEs associated with sodium oxybate treatment have been previously reported in pooled clinical trial data[3] and post-marketing data.[14] In this post-authorization study, the incidence of depression was 4.3%, compared with 7% in clinical trials.[3] Discontinuation of treatment due to depression occurred in <1% of patients both in the clinical trials[3] and in this post-authorization study. Among 670 patients with narcolepsy type 1 in this post-authorization study, there were two suicide attempts (including one patient with a history of depression) and one case of suicidal depression; all cases resolved. These findings are in line with the observed two suicides and two attempted suicides (including three patients with a history of depression) in 781 patients in the clinical trials.[3] Post-marketing monitoring has identified further cases of suicide and overdose of sodium oxybate with suicidal intent, mostly occurring in patients with risk factors such as previous history of suicide attempts.[14,15] While suicide attempts are uncommon, these observations highlight the requirement for monitoring patients for emergence of depressive symptoms during treatment, particularly those with relevant medical history. Dose-related confusion was reported by 1.5% of patients in this study versus 3% of patients in clinical trials.[3] There are limited case reports in the literature of parasomnias potentially related to treatment with sodium oxybate.[14,18] Sleep-related TEAEs have been reported in clinical trials, particularly at higher doses, although the incidence of sleepwalking was similar in patients treated with sodium oxybate and placebo, and it is unknown whether all reported episodes were true somnambulism.[3] Sleepwalking was the most common sleep-related TEAE in this post-authorization study (3.1%), followed by sleep-related eating disorder (0.9%) and sleep talking (0.7%).

The pharmacokinetics, efficacy, and safety of sodium oxybate have not yet been established in paediatric patients. Preliminary results from a recent double-blind, placebo-controlled study of sodium oxybate in children and adolescents aged 7–16 y who had narcolepsy with cataplexy showed a significant reduction in weekly cataplexy attacks and a safety profile similar to that observed previously.[19] In this post-authorization study, 54 patients were children and adolescents aged between 6 and 17 y. There are no specific dosing recommendations for children, but it was noted that the median dose in this subgroup was lower than that used in the overall population. No additional safety concerns were identified in paediatric patients.

Previous clinical studies of sodium oxybate have included insufficient numbers of elderly patients to allow evaluation of the safety profile in this population. In a limited number of elderly patients, the pharmacokinetics of sodium oxybate were not different to those in younger patients; no dose adaptations are required for elderly patients.[10] In this post-authorization study, 57 patients were aged between 66 and 79 y; this subgroup received the same median dose as the overall population. There was no evidence of any additional safety concerns in elderly patients.

GHB has been used as a drug of abuse for several decades, although there is evidence that the prevalence is declining.[11] Although sodium oxybate differs from illicit GHB in accessibility and purity, it is important to monitor the prevalence of any abuse of sodium oxybate. Human drug abuse potential studies of sodium oxybate have shown that positive drug effects are accompanied by negative effects such as nausea and gastrointestinal distress.[11] Prior to this report, the most recent post-marketing data available for sodium oxybate covered the period between market introduction in 2002 and March 2008, during which approximately 26,000 patients received sodium oxybate in Europe, the USA, and Canada.[14] During this

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period, there were 10 cases (0.039%) of Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV substance abuse, four cases (0.016%) of DSM-IV substance dependence, and two cases (0.008%) of confirmed sodium oxybate-facilitated sexual assault. Among an estimated 600,000 distributed bottles of sodium oxybate, there were five (0.0009%) confirmed incidents of diversion to an individual other than the patient. Although post-marketing data may be subject to under-reporting, it was concluded that sodium oxybate is associated with a low risk of abuse and dependence. Results of this post-authorization study are consistent with a low risk of abuse, with one reported case of intentional drug misuse by an individual other than the patient.

This post-authorization surveillance study was limited by its observational nature.

In conclusion, this large post-authorization, non-interventional surveillance study has provided real-world data on the use of sodium oxybate for the treatment of narcolepsy in clinical practice across Europe. Prescribing recommendations for indication and dosage were generally adhered to. Most patients complied with instructions – although a substantial proportion of patients consumed alcohol, took the medication <2 h after food, and did not adhere to the recommended time schedule, there were few associated TEAEs. The overall safety profile was consistent with that observed previously. The incidence of abuse was low.

Abbreviations

AE, adverse event; BMI, body mass index; CNS, central nervous system; ITT, intent to treat; EMA, European Medicines Agency; GHB, gamma-hydroxybutyrate; PI, prescribing information; SD, standard deviation; SPC, summary of product characteristics; TEAE, treatment-emergent adverse event.

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Disclosure statement

Geert Mayer, Giuseppe Plazzi, Álex Iranzo, Juan Ortega-Albás, and Timothy Quinnell were Principal Investigators for this study. Geert Mayer is a member of advisory boards for UCB Pharma, and Bioprojet. Giuseppe Plazzi has acted as a consultant for UCB Pharma, Jazz Pharmaceuticals, and Bioprojet. Juan Ortega-Albás has declared no conflicts of interest.

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Timothy Quinnell has received travel and subsistence expenses, and congress registration fees from UCB Pharma. Hanna Pesch, Pedro Serralheiro, and Didier Wuiame are employees of UCB Pharma. Anne-Françoise Schlit and Jürgen Bentz are employees and shareholders of UCB Pharma.

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Figure 1. Patient disposition

Other indications were narcolepsy (n = 24), narcolepsy without cataplexy (n = 23), idiopathic hypersomnia (n = 11), and other (n = 2).

Figure 2. Kaplan–Meier plot of treatment persistence for patients with narcolepsy type 1 (ITT population, N = 670)

Patients were censored at the date of the last available information. If data for any patient were collected for longer than 18 months, a cut-off of 18 months + 30 days was applied

ITT, intent to treat

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Table 1. Treatment compliance checklist responses completed by the physician for patients with narcolepsy type 1 (ITT population, N = 670)

Treatment compliance checklist item	Incidence (%)[a]	TEAEs rated by the investigator as associated with checklist items: each reported by one patient (1/670, 0.1%)[b]
Has the patient been taking sodium oxybate < 2 h after eating?	129/667 (19.3)	Dry mouth Agitation Circulatory collapse
Has the patient been taking sodium oxybate not according to recommended time schedule?	181/667 (27.1)	Nausea Decreased appetite Cataplexy Dizziness Somnolence Abnormal behavior Night sweats
Has the patient been taking alcohol?	237/667 (35.5)	Alcohol poisoning Insomnia Cough Suffocation feeling
Did the patient take sodium oxybate at least once at a frequency greater than two nightly doses?	21/667 (3.1)	None
Did the patient take sodium oxybate at least once at a dose of > 4.5 g per intake or > 9 g nightly?	17/667 (2.5)	Overdose Dizziness Enuresis
Did the patient experience difficulty preparing the dose resulting in an uncertain quantity ingested?	8/667 (1.2)	Inappropriate schedule of drug administration[c]
Did you receive a premature request from the patient for refills of sodium oxybate?	4/667 (0.6)	Upper abdominal pain[c]
Did you receive a request from the patient for dose adjustment not appropriate for their symptoms?	8/667 (1.2)	Anxiety Depression Nervousness
Did the patient continue use of sodium oxybate despite your recommendation to stop the drug?	0/293	None
Have you become aware of accidental or deliberate use of sodium oxybate by others in the patient's household?	1/667 (0.1)	Intentional drug misuse[c]

[a]Incidences are based on the number of patients who reported the item at least once during the study

[b]Associated TEAEs were those recorded by the investigator on the treatment compliance checklist and were defined as clinically significant symptoms that resulted from items in the checklist. Each TEAE was reported by one patient; one patient may have had more than one TEAE

[c]Serious TEAE

ITT, intent to treat; TEAE, treatment-emergent adverse event.

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Table 2. Overall summary of TEAEs for patients with narcolepsy type 1 (ITT population, N = 670)

	Number of patients (%)
At least one TEAE	451 (67.3)
Drug-related TEAE	291 (43.4)
TEAE leading to drug discontinuation	59 (8.8)
Severe TEAE	91 (13.6)
Serious TEAE	43 (6.4)
Deaths	1 (0.1)
TEAEs reported by ≥5% of patients	
Headache	78 (11.6)
Nasopharyngitis	43 (6.4)
Decreased weight	35 (5.2)
Dizziness	35 (5.2)
Nausea	34 (5.1)

ITT, intent to treat; TEAE, treatment-emergent adverse event.

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Table 3. TEAEs of special interest for patients with narcolepsy type 1 (ITT population, N = 670)

	Number of patients (%)
At least one TEAE of special interest	188 (28.1)
TEAEs of special interest reported by ≥ 3 patients	
Decreased weight	35 (5.2)
Depression	29 (4.3)
Somnambulism	21 (3.1)
Enuresis	18 (2.7)
Urinary incontinence	16 (2.4)
Confusional state	10 (1.5)
Depressed mood	9 (1.3)
Irritability	9 (1.3)
Aggression	6 (0.9)
Sleep-related eating disorder	6 (0.9)
Dyspnea	5 (0.7)
Nocturia	5 (0.7)
Sleep talking	5 (0.7)
Confusional arousal	4 (0.6)
Increased weight	4 (0.6)
Sleep apnea syndrome	4 (0.6)
Altered mood	3 (0.4)
Disorientation	3 (0.4)
Emotional disorder	3 (0.4)
Feeling abnormal	3 (0.4)
Hypothyroidism	3 (0.4)
Restlessness	3 (0.4)

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The following TEAEs of special interest were reported by two patients (0.3%) each: alcohol poisoning, agitation, eating disorder, epilepsy (epileptic seizure), myoclonus, suicide attempt.

The following TEAEs of special interest were reported by one patient (0.1%) each: adjustment disorder with mixed anxiety and depressed mood, amnesia, auditory hallucination, balance disorder, bipolar disorder, blood 1,25-dihydroxycholecalciferol decreased, bronchospasm, bruxism, delusion, depersonalization/decreolization disorder, emotional distress, hypoglycemia, hypomania, intentional product misuse, mental disorder, muscular weakness, overdose, panic attack, psychotic disorder, respiratory distress, schizophrenia, seizure, stress urinary incontinence, suffocation feeling, suicidal depression, toxicity to various agents, type 2 diabetes mellitus, weight fluctuation, weight loss diet.

ITT, intent to treat; TEAE, treatment-emergent adverse event.

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Table 4. TEAEs in patients aged <18 or >65 y for patients with narcolepsy type 1 (ITT population)

	Number of patients (%)	
	<18 y (N = 54)	**>65 y (N = 57)**
At least one TEAE	36 (66.7)	42 (73.7)
TEAEs reported by ≥5% of patients aged <18 y		
Headache	6 (11.1)	2 (3.5)
Enuresis	4 (7.4)	2 (3.5)
Nasopharyngitis	4 (7.4)	2 (3.5)
Decreased appetite	3 (5.6)	0
Decreased weight	3 (5.6)	4 (7.0)
Oropharyngeal pain	3 (5.6)	0
TEAEs reported by ≥5% of patients aged >65 y		
Dizziness	2 (3.7)	5 (8.8)
Decreased weight	3 (5.6)	4 (7.0)
Nausea	2 (3.7)	4 (7.0)
Back pain	0	3 (5.3)
Depression	0	3 (5.3)
Fall	0	3 (5.3)

ITT, intent to treat; TEAE, treatment-emergent adverse event.

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Table 5. TEAEs in patients with narcolepsy type 1 and a history of underlying sleep apnea (ITT population, N = 87)

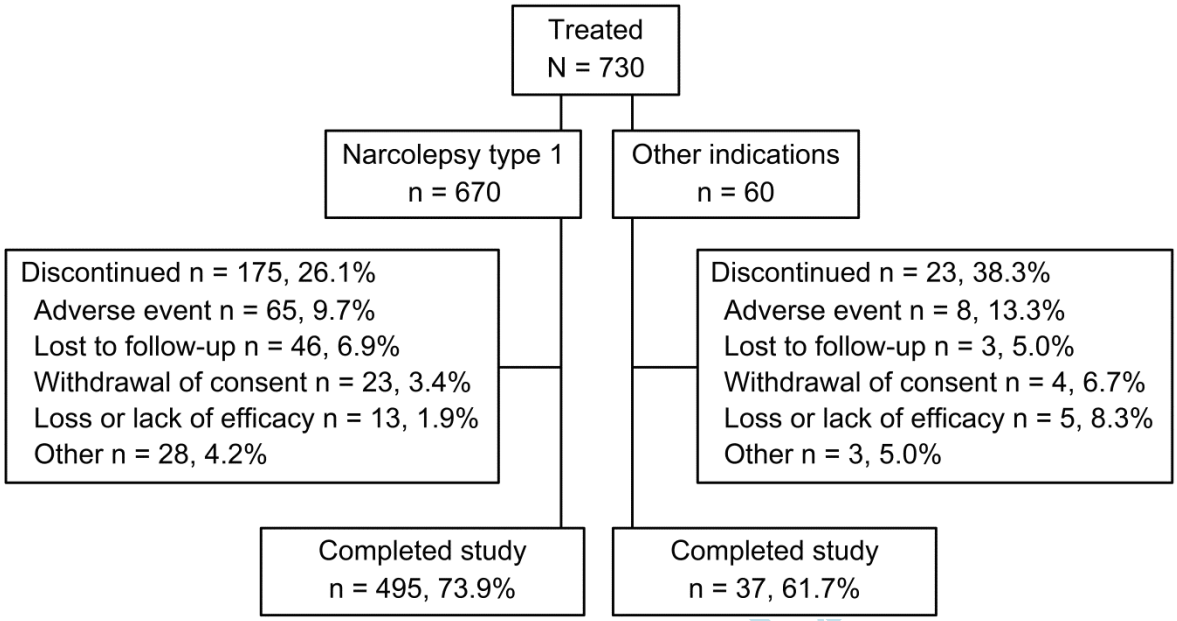
	Number of patients (%)
At least one TEAE	61 (70.1)
TEAEs reported by ≥ 5% of patients	
Headache	12 (13.8)
Nasopharyngitis	6 (6.9)
Depression	5 (5.7)

ITT, intent to treat; TEAE, treatment-emergent adverse event.

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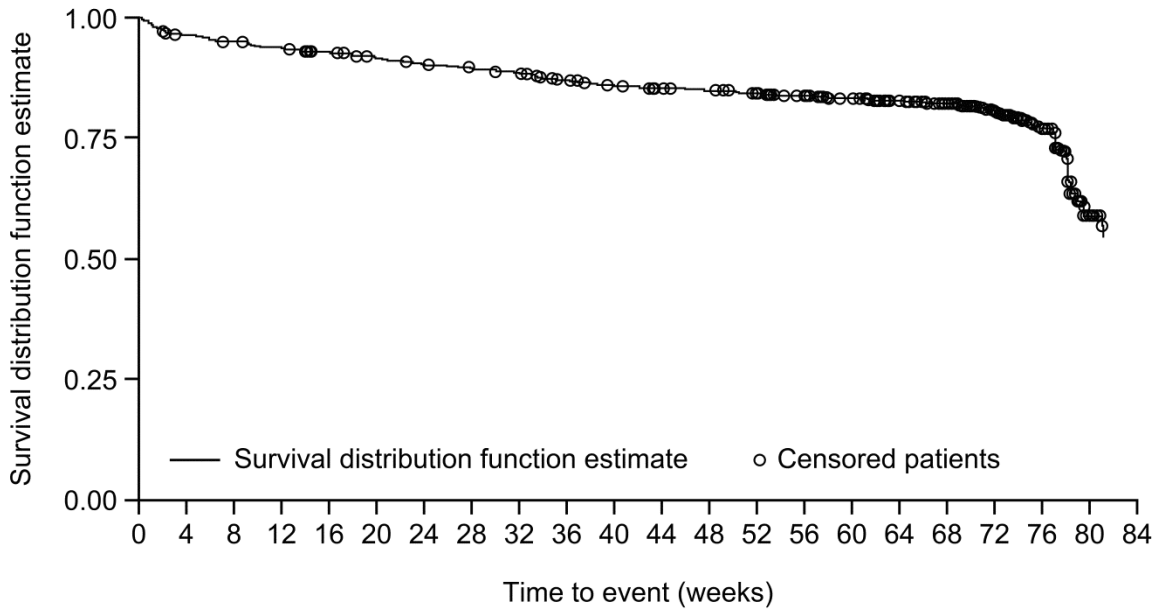
Figure 1.



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Figure 2.



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