



Calcium, Magnesium, Potassium and Sodium Oxybates (Xywav[®]) in Sleep Disorders: A Profile of Its Use

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Abstract

Calcium, magnesium, potassium and sodium oxybates (Xywav[®]; hereafter referred to as lower-sodium oxybate), a new oxybate formulation with a greatly reduced sodium burden compared with previously approved sodium oxybate (Xyrem[®]), is approved for the treatment of cataplexy and excessive daytime sleepiness (EDS) in adults and children aged ≥ 7 years with narcolepsy, and is the first drug approved for the treatment of idiopathic hypersomnia in adults in the USA. In two pivotal, double-blind, placebo-controlled, phase 3 trials of randomized-withdrawal design, lower-sodium oxybate effectively improved cataplexy and EDS in adults with narcolepsy, and EDS and overall idiopathic hypersomnia symptoms in adults with idiopathic hypersomnia during open-label titration and optimization periods. At the end of the double-blind, randomized withdrawal period, participants randomized to switch to placebo experienced significant worsening in these symptoms compared with those randomized to continue lower-sodium oxybate. Furthermore, worsening in patient- and clinical-rated global scales, as well as measures of health-related quality of life were also seen with placebo versus lower-sodium oxybate. Lower-sodium oxybate is generally well tolerated, with the tolerability profile being largely consistent to that seen with sodium oxybate.

Plain Language Summary

Narcolepsy and idiopathic hypersomnia are rare, chronic sleep disorders that can debilitate patients' cognitive function, social functioning and health-related quality of life. They are primarily characterized by excessive daytime sleepiness (EDS) and often require long-term (even life-long) treatment to reduce symptoms and improve functioning. Sodium oxybate (Xyrem[®]) is an effective treatment option for cataplexy and EDS in patients with narcolepsy; however, its high sodium content may put patients at higher risk of increased blood pressure and cardiovascular disease. To reduce the excessive sodium intake associated with long-term therapy, lower-sodium oxybate (Xywav[®]), a new oxybate formulation with 92% less sodium content, has been developed. In the USA, it is approved for the treatment of cataplexy or EDS in adults and children aged ≥ 7 years with narcolepsy, and is the first drug approved for the treatment of idiopathic hypersomnia in adults. In pivotal phase 3 trials, following dose titration and optimization periods, participants randomized to discontinue lower-sodium oxybate and take placebo showed significant worsening in narcolepsy- and idiopathic hypersomnia-related symptoms, as well as health-related quality of life outcomes compared with participants randomized to continue lower-sodium oxybate. Lower-sodium oxybate is generally well tolerated, with its safety profile similar to that of sodium oxybate. Lower-sodium oxybate is a valuable treatment option for children and adults with narcolepsy and adults with idiopathic hypersomnia.

Digital Features for this Adis Drug Q&A can be found at <https://doi.org/10.6084/m9.figshare.19142984>

Adis evaluation of lower-sodium oxybate in sleep disorders

A novel oxybate formulation with same active moiety and 92% less sodium content than sodium oxybate.

First drug approved for the treatment of idiopathic hypersomnia in adults.

Effectively improves narcolepsy- and idiopathic hypersomnia-related symptoms, and health-related quality of life outcomes.

Generally well tolerated.

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1 What is the Rationale for Developing Lower-Sodium Oxybate?

Narcolepsy and idiopathic hypersomnia are rare, chronic sleep disorders that can debilitate patients' cognitive function, social functioning and health-related quality of life (HR-QOL) [1–3]. They are primarily characterized by excessive daytime sleepiness (EDS), with many narcolepsy patients also manifesting cataplexy. Additionally, disturbed nocturnal sleep, hypnagogic and hypnopompic hallucinations, and sleep paralysis can be seen in narcolepsy, and prolonged night time sleep and sleep inertia can be seen in idiopathic hypersomnia [1–3].

Narcolepsy and idiopathic hypersomnia often require long-term (even life-long) treatment to reduce symptoms and improve functioning [1–4]. The choice of appropriate medications should be based on several patient (e.g. age, comorbidities) and drug (e.g. efficacy and safety profiles, abuse potential, convenience of administration and costs) characteristics [1–5]. American Academy of Sleep Medicine (AASM) practice guideline and European narcolepsy guideline recommend several wake-promoting agents with varying mechanisms of actions, and stimulants for the management of central hypersomnolence disorders, including narcolepsy and idiopathic hypersomnia [4, 5]. Of note, pharmacological agents currently recommended for idiopathic hypersomnia by AASM guideline are not specifically approved for this indication [4].

Sodium oxybate (Xyrem®) oral solution has been approved for the treatment of cataplexy and EDS in patients aged ≥ 7 years with narcolepsy [6]. The efficacy and safety of sodium oxybate for the treatment of narcolepsy are well established and have been extensively reviewed [7, 8]. In AASM practice guideline, based on available evidence, sodium oxybate is given a strong recommendation for treating narcolepsy in adults and a conditional recommendation for treating narcolepsy in children and idiopathic hypersomnia in adults [4]. Sodium oxybate is also given a strong recommendation for the treatment of cataplexy and EDS in children and adults with narcolepsy in European narcolepsy guideline [5]. At the recommended dosages, sodium oxybate can increase daily sodium intake by 1100–1640 mg [6], which is $> 70\%$ of recommended maximum sodium daily intake [9, 10]. Long-term exposure to high sodium-containing drugs may increase blood pressure and cardiovascular risk [11, 12]. Furthermore, patients with narcolepsy often have comorbidities or risk factors that may contribute to increased risk of cardiovascular disease [9–11].

Given that sodium oxybate is usually a long-term (even life-long) treatment for patients with central hypersomnolence disorders, a new oxybate formulation that contains

the same active moiety with lower sodium content would help patients reduce excessive sodium intake and thereby potentially lower the risk of high blood pressure and cardiovascular disease [10, 13]. Calcium, magnesium, potassium and sodium oxybates (Xywav®; hereafter referred to as lower-sodium oxybate) is an oral solution that has a unique composition of cations, containing 92% less sodium than the previously approved sodium oxybate oral solution [10, 13, 14]. In the USA, lower-sodium oxybate has been granted orphan drug exclusivity for narcolepsy and idiopathic hypersomnia and has been acknowledged as clinically superior to sodium oxybate for its significant chronic sodium burden reduction, which may be clinically meaningful in lowering cardiovascular morbidity in patients for whom the drug is indicated [15].

2 For Whom is Lower-Sodium Oxybate Indicated?

In the USA, lower-sodium oxybate is approved for the treatment of cataplexy and EDS in adults and children aged ≥ 7 years with narcolepsy, and is the first drug approved for the treatment of idiopathic hypersomnia in adults [14]. Due to the risks of CNS depression, and abuse and misuse, lower-sodium oxybate is only available through a restricted distribution program called Xywav and Xyrem Risk Evaluation Mitigation Strategy under which the drug is prescribed and dispensed by a specially certified healthcare professional and a central pharmacy, and is only available to patients enrolled in the program. Risk management strategies should be followed to reduce the potential for misuse and abuse [14]. An overview of its use for the treatment of narcolepsy and idiopathic hypersomnia is provided in Table 1, with the recommended dosing regimens shown in Fig. 1. Consult local prescribing information for further details.

3 How Does Lower-Sodium Oxybate Work?

Lower-sodium oxybate, a CNS depressant, is a mixture of calcium oxybate, magnesium oxybate, potassium oxybate and sodium oxybate [γ -hydroxybutyrate (GHB); is an endogenous compound of the neurotransmitter GABA] [14]. Although the mechanism of action of lower-sodium oxybate for the treatment of narcolepsy and idiopathic hypersomnia is not fully elucidated, it is hypothesized to involve GABA_B actions at noradrenergic, dopaminergic and thalamocortical neurons during sleep [14].

4 What is the Pharmacokinetic Profile of Lower-Sodium Oxybate?

The pharmacokinetics of lower-sodium oxybate are similar between healthy individuals and patients with narcolepsy or idiopathic hypersomnia [14]. Although the pharmacokinetics of lower-sodium oxybate have not been evaluated in children, the pharmacokinetics of sodium oxybate in children are similar to those observed in adults [14].

The pharmacokinetics of GHB are non-linear and similar following single or multiple doses [14]. Following oral administration of lower-sodium oxybate in the fasted state, peak plasma concentration (C_{\max}) is reached in 1.3 h in healthy individuals, with the plasma level of GHB increasing more than dose-proportionally across doses of 2.25–4.5 g [14]. Greater dose-proportionality for area under the curve (AUC) of lower-sodium oxybate was demonstrated in patients with idiopathic hypersomnia at total nightly doses of 3–9 g [16]. Oral administration of lower-sodium oxybate with a high-fat meal reduced the C_{\max} and AUC of GHB by 33% and 16%, respectively [14].

In two phase 1 pharmacokinetic studies in healthy individuals, in the fasted state, lower-sodium oxybate demonstrated bioequivalence to sodium oxybate in terms of AUC, but not C_{\max} [17]. At equivalent doses, lower-sodium oxybate had a lower C_{\max} , delayed time to reach C_{\max} and similar AUC versus sodium oxybate. The lower sodium content relative to sodium oxybate is likely to be the cause of these pharmacokinetic differences [17].

GHB has an apparent volume of distribution of 190–384 mL/kg, with < 1% bound to plasma proteins over the GHB concentrations of 3–300 $\mu\text{g/mL}$ [14]. GHB is primarily metabolized to carbon dioxide and water via the tricarboxylic acid (Krebs) cycle; β -oxidation also contributes to the biotransformation of GHB. The clearance of GHB is primarily via biotransformation to carbon dioxide, which is then eliminated by expiration. Overall, < 5% of unchanged drug appears in human urine within 6–9 h after dosing. GHB has a terminal elimination half-life of 0.66 h [14].

Lower-sodium oxybate pharmacokinetics did not appear to be affected to any clinically relevant extent by sex [14]. The elimination half-life of GHB is prolonged in cirrhotic patients. Hence, the starting dose of lower-sodium oxybate should be reduced in patients with hepatic impairment (Table 1) [14]. According to population pharmacokinetic analyses, body weight is the major intrinsic factor affecting the pharmacokinetics of GHB [14, 18]. Subsequently, the recommended dosage of lower-sodium oxybate in children should be based on body weight (Fig. 1) [14].

In vitro studies indicate that clinically significant interactions between sodium oxybate and CYP enzymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1

and CYP3A are not expected [14]. In drug-drug interaction studies in healthy individuals, coadministration of sodium oxybate with divalproex sodium increased mean systemic exposure of GHB, while no significant differences were observed when the drug was coadministered with diclofenac or ibuprofen. An initial dose reduction of lower-sodium oxybate is recommended when the drug is used concomitantly with divalproex sodium (Table 1) [14].

5 What is the Clinical Efficacy of Lower-Sodium Oxybate?

The clinical efficacy of lower-sodium oxybate in the treatment of narcolepsy ($n = 134$ [19]) and idiopathic hypersomnia ($n = 115$ [20]) in adults was evaluated in two separate, pivotal, double-blind, placebo-controlled, phase 3 trials of randomized-withdrawal design. Participants with narcolepsy [based on International Classification of Sleep Disorders (ICSD) 3rd edition or Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria] were required to have a history of ≥ 14 cataplexy attacks in a typical 2-week period prior to receiving any narcolepsy treatment [19]. Participants with idiopathic hypersomnia (based on ICSD 2nd or 3rd edition criteria) were required to have an average nocturnal total sleep time of ≥ 7 h and an Epworth Sleepiness Scale (ESS) score of ≥ 11 at study entry [20]. Participants were either treatment-naïve or were taking medications, including sodium oxybate and/or other medications, for their symptoms at study entry [19, 20]. Participants taking sodium oxybate at study entry were required to have shown clinical improvement of cataplexy and EDS in participants with narcolepsy, and EDS in participants with idiopathic hypersomnia [19, 20].

These multinational studies included a ≤ 30 -day screening period, followed by a 12-week [19] or a 10–14 week [20] open-label optimized treatment and titration period (OLOTP) during which participants received the approved dosages of lower-sodium oxybate (Fig 1) [19, 20]. During OLOTP, participants with narcolepsy tapered and discontinued all other antiepileptics while alerting agent use was maintained [19]; participants with idiopathic hypersomnia were allowed to maintain stable use of alerting agents and no medications were tapered or withdrawn [20]. Participants continued to receive their individually optimized doses of lower-sodium oxybate for a further 2-week stable-dose period (SDP) before entering a 2-week, double-blind, randomized withdrawal period (DBRWP), in which participants were randomized to continue lower-sodium oxybate or switch to placebo. Randomization was stratified by treatment at study entry. Participants who completed DBRWP were eligible to enter a 24-week open-label safety extension period [19, 20].

Table 1 Prescribing summary of lower-sodium oxybate (Xywav®) in sleep disorders in the USA [14]**How is lower-sodium oxybate available?**

Oral solution containing 0.5 g of total salt concentration (0.234 g calcium oxybate, 0.096 g magnesium oxybate, 0.13 g potassium oxybate and 0.04 g sodium oxybate) per mL

How should lower-sodium oxybate be administered?

Dose preparation	Prepare dose(s) before bedtime; dilute with ≈ 60 mL of water in the empty pharmacy-provided containers before ingestion Prepared solution must be taken within 24 h
Administration	At least 2 h after eating Narcolepsy: two doses, with the first taken at bedtime and the second 2.5–4 h after the first (may need to set an alarm to awaken) Idiopathic hypersomnia: take as one or two doses at bedtime; if divided into two doses, take the second dose 2.5–4 h after the first dose (may need to set an alarm to awaken)
Administration instruction	Take each dose while in bed and lie down immediately thereafter as the drug may cause patients to fall asleep without feeling drowsy

Refer to Fig. 1 for recommended dosing regimens

What are the contraindications to the use of lower-sodium oxybate?

Coadministration with sedative hypnotics or alcohol, or patients with succinic semialdehyde dehydrogenase deficiency

How should lower-sodium oxybate be used in special populations?

Patients with hepatic impairment	Due to ↑ exposure, ↓ dosage by half
Patients with renal impairment	No studies in these patients
Pregnancy	Insufficient data in humans; animal studies show ↑ stillbirths, ↓ offspring postnatal viability and growth
Breast feeding	Insufficient data but GHB excreted in human milk following oral administration
Children	Efficacy and safety for children with idiopathic hypersomnia and children aged < 7 years with narcolepsy not established

What other special warnings/precautions/monitoring requirements pertain to the use of lower-sodium oxybate?

CNS depression	Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination for at least 6 h after taking lower-sodium oxybate
Abuse and misuse	Classified as schedule III controlled substance; evaluate patients with recent history of abusing drugs carefully and monitor closely for signs of abuse/misuse (e.g. ↑ in strength or frequency of dosing, feigned cataplexy and drug-seeking behaviour)
Respiratory depression and sleep-disordered breathing	May impair respiratory drive, especially in patients with compromised respiratory function Physicians should be aware that lower-sodium oxybate administration may ↑ central apnoea and clinically relevant oxygen desaturations events Sleep-related breathing disorders may be more prevalent in patients who are obese, men, postmenopausal women not on hormone replacement therapy and those with narcolepsy
Depression and suicidality	Monitor carefully for the emergence of depressive symptoms during treatment, especially in patients with a previous history of a depressive illness and/or suicide attempts
Other behavioural or psychiatric adverse reactions	Monitor for the emergence/increase of behavioural or psychiatric symptoms such as confusion, anxiety, and hallucinations
Parasomnias	Parasomnias, including sleep walking, may occur during treatment; monitor and fully evaluate episodes of sleep walking and consider appropriate interventions

What are the potential clinically relevant interactions between lower-sodium oxybate and other drugs?

Divalproex sodium	Concomitant use ↑ systemic exposure of GHB; ↓ an initial dose of lower-sodium oxybate and monitor patient response and adjust dose accordingly
CNS depressants	Coadministration with other CNS depressants (e.g. opioid analgesics, benzodiazepines, sedating anti-depressants, antipsychotics or anti-epileptic drugs, general anaesthetics, muscle relaxants and/or illicit CNS depressants) may ↑ the risk of respiratory depression, hypotension, profound sedation, syncope and death; consider dose reduction or discontinuation of ≥ 1 CNS depressants if used concomitantly Consider interrupting lower-sodium oxybate treatment if short-term opioid use is required

GHB gamma-hydroxybutyrate, ↑ increase(s/d), ↓ decrease(s/d)

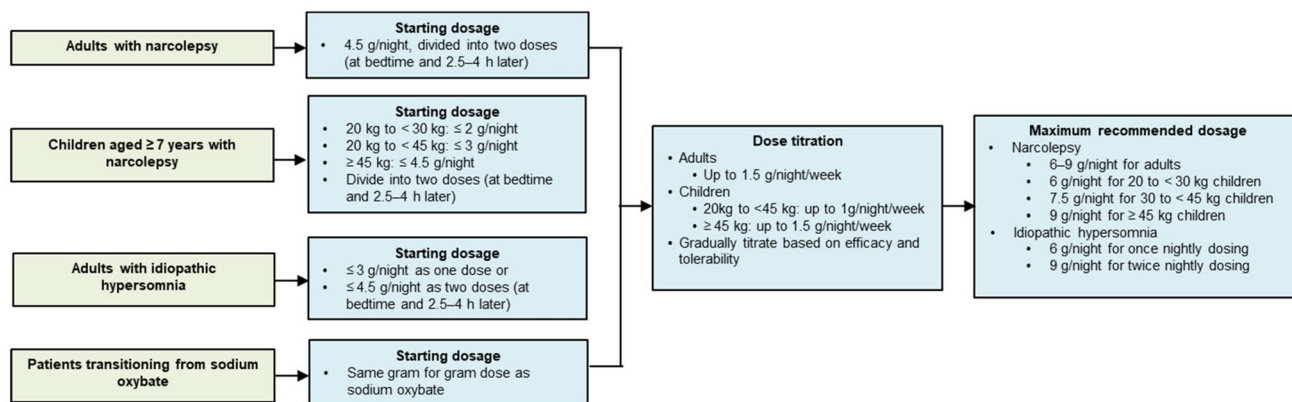


Fig. 1 Recommended dosing regimens of lower-sodium oxybate for the treatment of narcolepsy and idiopathic hypersomnia, based on prescribing information in the USA [14]

There are no studies on the use of lower-sodium oxybate in children aged ≥ 7 years with narcolepsy as its efficacy has been well established with sodium oxybate [14, 21].

5.1 In Participants with Narcolepsy

During OLOTTP, sodium oxybate-experienced participants at study entry initiated lower-sodium oxybate treatment at the same dose of sodium oxybate for the first 2 weeks, while sodium oxybate-naïve participants at study entry initiated treatment with lower-sodium oxybate 4.5 g/night, divided into two doses [19]. Based on efficacy and tolerability, the doses of lower-sodium oxybate could be adjusted and titrated up to 1.5 g/night/week to a maximum total nightly dosage of 9 g/night, divided in two doses [19]. Overall, most participants who transitioned from sodium oxybate to lower-sodium oxybate did not require dose adjustments and participants who were sodium oxybate-naïve achieved an optimized dose of lower-sodium oxybate within three dose adjustments [22]. The median stable nightly dosage of lower-sodium oxybate was 7.0–9.0 g/night [22].

In adults with narcolepsy, a reduction in number of cataplexy attacks and ESS score was demonstrated with lower-sodium oxybate during OLOTTP, with these improvements maintained during SDP and remaining similar across participants prior to randomization [19]. Of note, over the course of OLOTTP, the number of cataplexy-free days per week varied based on treatment at study entry, but prior to randomization it was similar across participants [19, 23].

At the end of DBRWP, participants randomized to discontinue lower-sodium oxybate and take placebo showed significant worsening in weekly number of cataplexy attacks (primary endpoint) and change in ESS score (key secondary endpoint) compared to participants who continued taking lower-sodium oxybate (Table 2) [19]. Furthermore, the proportion of participants experiencing worsening in

Patient Global Impression of Change (PGI-C) and Clinical Global Impression of Change (CGI-C) scores was significantly higher with placebo than with lower-sodium oxybate (Table 2). The median number of cataplexy-free days per week was higher in lower-sodium oxybate than placebo recipients (> 5 days/week vs 3.5 days/week) [19].

The beneficial effects of lower-sodium oxybate on HR-QoL [measured by the 36-item Short-Form Health Survey (SF-36) and EuroQoL EQ-5D-5L] were maintained during the study [19, 24]. At the end of DBRWP, a decrease (indicative of HR-QoL deterioration) in the SF-36 vitality, role-physical and general health subscale scores, as well as the EQ-5D-5L visual analog scale (VAS) score was seen with placebo versus lower-sodium oxybate (nominal $p \leq 0.0277$). Changes in the EQ-5D-5L crosswalk index score were minimal in both treatment groups [19, 24].

There are no studies on the use of lower-sodium oxybate in children aged ≥ 7 years with narcolepsy as its efficacy has been well established with sodium oxybate [14, 21]. In a double-blind, placebo-controlled, randomized-withdrawal phase 3 study, 104 children aged 7–16 years with narcolepsy with cataplexy underwent a 1-week titration period, during which sodium oxybate-naïve participants received sodium oxybate therapy, with doses initiated, titrated and stabilised based on body weight, efficacy and tolerability, followed by a 2-week SDP; sodium oxybate-experienced participants underwent a 3-week SDP. Afterwards, participants entered a 2-week DBRWP in which 63 children were randomized to continue sodium oxybate or switch to placebo. At the end of DBRWP, sodium oxybate was associated with significantly ($p \leq 0.0004$) more favourable outcomes than placebo in terms of the median change in weekly number of cataplexy attacks (0.3 vs 12.7; primary endpoint) and ESS scores (0 vs 3; key secondary endpoint), as well as the proportion of participants experiencing worsening in CGI-C cataplexy

Table 2 Efficacy of lower-sodium oxybate for the treatment of narcolepsy and idiopathic hypersomnia in adults in phase 3 studies [19, 20]

Comparators (no. of pts)	Change from SDP to DBRWP (BGD; 95% CI ^a)			Pts (%) with worsening ^b PGI-C score at the end of DBRWP ^c	Pts (%) with worsening ^b CGI-C score at the end of DBRWP
	No of weekly cataplexy attacks ^c	ESS score ^d	IHSS score ^e		
Narcolepsy [19]					
PL (65)	11.46	3.0	NA	44.6	60.0
LXB (69)	0.12*(-3.3; -6.0, -1.5)	0.0*(-2.0; -4.0, -1.0)	NA	4.3* ^f	5.9* ^f
Idiopathic hypersomnia [20]					
PL (59)	NA	7.4	13.3	88	88
LXB (56)	NA	0.7*(-6.5; -8.0, -5.0)	1.4*(-12.0; -15.0, -8.0)	21*	21* ^f

In participants with narcolepsy, the mean weekly number of cataplexy attacks was 7.2–8.9 and the mean ESS score was 12.6–13.6 at the end of SDP [14]; in participants with idiopathic hypersomnia, the mean ESS score was 5.8–6.3 and the mean IHSS score was 15.2–15.5 at the end of SDP [20]

BGD between-group difference, CGI-C Clinical Global Impression of Change, DBRWP double-blind randomized withdrawal period, ESS Epworth Sleepiness Scale, IHSS Idiopathic Hypersomnia Severity Scale, LXB lower-sodium oxybate, NA not applicable, PGI-C Patient Global Impression of Change, PL placebo, pts participants, SDP stable-dose period

* $p < 0.0001$ vs PL

^aEstimated median difference [20] or location shift [19] between the treatment groups, and asymptotic 95% CI using the Hodges-Lehmann estimator were reported, except in change in ESS score in participants with idiopathic hypersomnia where least-square mean difference was reported

^bIncludes ‘much’ or ‘very much’ worse for participants with narcolepsy [19] and ‘minimal’, ‘much’ or ‘very much’ worse for participants with idiopathic hypersomnia [20]

^cPrimary endpoint for participants with narcolepsy [19]

^dPrimary endpoint for participants with idiopathic hypersomnia [20] and key secondary endpoint for participants with narcolepsy [19]

^eKey secondary endpoint for participants with idiopathic hypersomnia [20]

^fNominal $p < 0.0001$

severity (17% vs 66%) and narcolepsy overall (10% vs 59%) scores [14, 21].

5.2 In Participants with Idiopathic Hypersomnia

During OLOTTP, participants were initiated on a twice nightly dosing regimen (≤ 4.5 g/night divided into two doses) or once nightly regimen (≤ 3 g/night at bedtime) at the discretion of the investigators [20]. Participants taking sodium oxybate at study entry initiated lower-sodium oxybate at the same dose and regimen. Changes in regimen (once or twice nightly) were allowed during OLOTTP. Afterwards, based on efficacy and tolerability, the doses of lower-sodium oxybate could be adjusted and titrated up to 1.5 g/night/week to a maximum total nightly dosage of 6 g/night for the once-nightly regimen and 9 g/night for the twice-nightly regimen [20]. At the end of SDP, the majority of participants (77%) were receiving the twice-nightly regimen; the total nightly dosage of lower-sodium oxybate was 4.5 g/night in participants receiving the drug once-nightly and 7.5 g/night for those receiving the drug twice-nightly [25].

In adults with idiopathic hypersomnia, improvements in ESS and Idiopathic Hypersomnia Severity Scale (IHSS [26]) scores were demonstrated with lower-sodium oxybate

during OLOTTP, with these improvements maintained during SDP and remaining similar across participants prior to randomization [20].

At the end of DBRWP, participants randomized to discontinue lower-sodium oxybate and take placebo showed a significant worsening in ESS (primary endpoint) and IHSS (key secondary endpoint) scores compared to participants who continued taking lower-sodium oxybate (Table 2) [20]. In addition, a significantly higher percentage of participants in the placebo group reported worsening in the PGI-C (key secondary endpoint) compared with the lower-sodium oxybate group (Table 2). Similarly, the proportion of participants reporting worsening in the CGI-C was lower with lower-sodium oxybate than with placebo (Table 2) [20].

Subgroup analyses, some of which were post hoc, indicated that beneficial effects of lower-sodium oxybate were evident regardless of idiopathic hypersomnia phenotype (with and without nighttime long sleep time), sex, dosage regimens (once- or twice-nightly) and baseline idiopathic hypersomnia treatment [20, 25].

In a post hoc analysis, lower-sodium oxybate reduced 24 h total sleep time, nocturnal sleep time and total nap duration during OLOTTP, including in participants with higher baseline 24 h total sleep time [27]. At the end of DBRWP,

24 h total sleep time worsened in participants who switched to placebo but remained stable in participants who continued taking lower-sodium oxybate [27].

Functional status, sleep inertia and work productivity (as measured by the Functional Outcomes of Sleep Questionnaire short version, the VAS for Sleep Inertia and the Work Productivity and Activity Impairment for Specific Health Problems, respectively) improved with lower-sodium oxybate, with these benefits maintained during DBRWP in participants randomized to continue lower-sodium oxybate and decreased in those randomized to switch to placebo (all nominal $p \leq 0.0092$) [20].

Longer-term, clinically meaningful improvements associated with lower-sodium oxybate in participants with idiopathic hypersomnia were maintained during the open-label extension period of up to 24 weeks [28, 29].

6 What is the Tolerability of Lower-Sodium Oxybate?

Lower-sodium oxybate is generally well tolerated, with its tolerability profile being largely consistent with that established for sodium oxybate [19, 20]. Given its similar safety profile to sodium oxybate in adults, the tolerability profile of lower-sodium oxybate in children is expected to be similar to that observed with sodium oxybate in children [14]. The US prescribing information carries a black box warning regarding the risk of CNS depression, and abuse and misuse of GHB [14]. Information on special warnings, precautions and management of selected adverse events of special interest with the use of lower-sodium oxybate are summarized in Table 1. Discussion in this section focuses on data relevant to the use of lower-sodium oxybate in adults who participated in the pivotal phase 3 studies.

The tolerability profile of lower-sodium oxybate was generally similar between participants with narcolepsy and those with idiopathic hypersomnia [19, 20]. In the pivotal phase 3 studies, 76.1% of 201 participants with narcolepsy and 80% of 154 participants with idiopathic hypersomnia had treatment-emergent adverse events (TEAEs) while receiving lower-sodium oxybate, with most being mild to moderate in severity [19, 20]. The majority of TEAEs tended to occur early after treatment initiation and decreased over time [14]. The most commonly ($\geq 10\%$) reported TEAEs included headache (20.4%), nausea (12.9%), dizziness (12.9%) and worsening cataplexy (10.0%) in participants with narcolepsy [19], and nausea (22%), headache (18%), dizziness (12%), anxiety (11%) and vomiting (11%) in participants with idiopathic hypersomnia [20].

In participants with narcolepsy, fewer TEAEs were reported in sodium oxybate-experienced participants at study entry than sodium oxybate-naïve participants at study

entry [30]. In participants with idiopathic hypersomnia, the incidence of TEAEs was similar regardless of whether participants were taking the once- or twice-nightly regimen, were treatment-naïve or -experienced, or were exposed to a single dose of lower-sodium oxybate > 4.5 g or not [20, 31].

Overall, serious TEAEs occurred in 3% of participants with narcolepsy and idiopathic hypersomnia, with two serious adverse events reported in participants with narcolepsy (confusion and hallucinations, increased muscle enzymes) and none reported in participants with idiopathic hypersomnia considered to be treatment-related [19, 20]. TEAEs led to treatment discontinuation in 10% and 17% of participants with narcolepsy and idiopathic hypersomnia, respectively, with most occurring during the first few weeks of treatment initiation [14, 19, 20]. The most common ($> 2\%$) TEAEs leading to treatment discontinuation included worsening cataplexy in participants with narcolepsy, and anxiety in participants with idiopathic hypersomnia. Depression and depressed mood were reported in $< 5\%$ of participants [14] and no participants reported TEAEs of suicidal ideation or suicidal behaviour [19, 20].

There were no clinically significant changes in laboratory parameters, physical examinations, or electrocardiograms with lower-sodium oxybate [19, 20].

Longer-term, the tolerability profile of lower-sodium oxybate in participants with idiopathic hypersomnia was similar to that observed in participants with narcolepsy and no new safety signals were identified [28, 29].

7 What is the Current Clinical Position of Lower-Sodium Oxybate?

Being the first drug approved for the treatment of idiopathic hypersomnia, lower-sodium oxybate oral solution is a valuable, effective and generally well-tolerated treatment option for children and adults with narcolepsy and adults with idiopathic hypersomnia. Given its lower sodium content (compared with sodium oxybate), lower-sodium oxybate may be more beneficial for patients with cardiovascular and/or metabolic comorbidities for whom high sodium daily intake can be harmful [1, 2]. In the USA, lower-sodium oxybate has been granted orphan drug exclusivity for narcolepsy and idiopathic hypersomnia [15].

Overall, clinical evidence from the pivotal phase 3 trials indicate that recommended dosages of lower-sodium oxybate (6–9 g/night) reduce the weekly number of cataplexy attacks and ESS score in participants with narcolepsy, and improve ESS and IHSS scores in participants with idiopathic hypersomnia. Furthermore, at the end of DBRWP, participants randomized to switch to placebo experienced significant worsening in these measurements compared with those randomized to continue lower-sodium oxybate.

Similarly, significant worsening in PGI-C and CGI-C scores, as well as measures of HR-QOL, functional status, sleep inertia and work productivity, were seen with placebo versus lower-sodium oxybate. Longer term, the clinical benefits of lower-sodium oxybate were maintained for up to 24 weeks of therapy. The drug is generally well tolerated, with the tolerability profile being largely consistent with that established for sodium oxybate. Of note, the randomized withdrawal design used in the trials enriches the trial population for responders to lower-sodium oxybate and thereby may affect the generalizability of the findings [20, 32].

Real-world studies and additional direct head-to-head clinical trials of different symptomatic treatment options for narcolepsy, such as armodafinil, modafinil, pitolisant and solriamfetol, would be helpful to further clarify the position of lower-sodium oxybate in the management of narcolepsy and idiopathic hypersomnia.

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