November 5, 2025
Institute for Clinical and Economic Review
14 Beacon St, Suite 800,
Boston, MA 02108

RE: Jazz response to the draft scope for ICER's assessment of oveporexton for narcolepsy

Dear ICER Review Team:

Jazz Pharmaceuticals, Inc. (Jazz) appreciates the opportunity to contribute to the Institute for Clinical and Economic Review (ICER) evaluation of oveporexton for the treatment of narcolepsy Type 1. Jazz is dedicated to advancing innovative therapies that transform the lives of patients and families affected by serious conditions. As a global, patient-focused, science-driven biopharmaceutical company, Jazz maintains a neuroscience portfolio with leading therapies for sleep disorders and rare epilepsies. In narcolepsy, Jazz brings more than 20 years of leadership in sleep medicine, with approved treatments, including Xyrem® and Xywav®, that address the 24-hour multi-symptom burden of disease such as disrupted nighttime sleep (DNS; fragmented nocturnal sleep marked by frequent awakenings and poor sleep continuity), excessive daytime sleepiness (EDS), and cataplexy.[1,2] Our research spans both clinically validated measures and real-world patient experiences, reflecting our commitment to rigorous science and meaningful improvements in care.

ICER's characterization of narcolepsy and its impact on patients is commendable. To further support ICER's commitment to an accurate and meaningful assessment, Jazz offers the following comments on current treatment approaches and comparative considerations for oveporexton.

Inclusion of Xyrem and Xywav as Comparators to Oveporexton Is Not Justified

Mechanistic Differences. Narcolepsy type 1, the focus of ICER's assessment, is a heterogenous neurological sleep disorder characterized by orexin deficiency and a constellation of sleep and daytime symptoms, including EDS, cataplexy, DNS, hallucinations, and sleep paralysis.[3] Oveporexton, a selective orexin receptor 2 agonist, may restore downstream neurotransmitter activity lost when endogenous orexin levels decline and was shown to improve wakefulness in preclinical models.[4,5] In stark contrast, sodium oxybate (Xyrem) and low-sodium oxybate (Xywav) act via GABA-B receptor modulation, resulting in enhanced slow-wave sleep, reduced sleep fragmentation, and more consolidated nocturnal sleep.[6] By improving sleep architecture, Xyrem and Xywav help restore more natural sleep patterns.

While Xyrem and Xywav do not directly restore orexin signaling, their ability to address both nighttime and daytime symptoms through sleep consolidation, and improvements in daytime functioning seen as reductions in EDS and cataplexy make them valuable components of narcolepsy management. Their role is distinct from, but potentially complementary to, different mechanism-based therapies like oveporexton, which target orexin deficiency and promote wakefulness. Given that Xywav affects nighttime and daytime symptoms while overporexton addresses daytime symptoms, it is possible that they may be used complementarily in clinical practice. As a result, Xyrem and Xywav are not suitable comparators for oveporexton, as each therapy is presumed to achieve its effects through distinct biological processes and, because this implies a forced choice between oveporexton and Xywav. Rather, clinical expertise and available

evidence dictates that the combined use of these drug classes in some patients will enable more complete 24-hour management of narcolepsy burden.

Place in Therapy. In contrast to daytime wake-promoting agents, Xyrem and Xywav target symptoms of narcolepsy by modulating disease processes during sleep. They are controlled under Schedule III and subject to Risk Evaluation and Mitigation Strategies (REMS), and together with administration at bedtime, occupy a unique place in therapy. A review of payer policies indicates that step therapy requirements are common.[7,8] Patients are typically required to try and fail authorized generics, wakefulness-promoting agents, and stimulants before accessing branded products. As oveporexton advances toward potential approval, it remains uncertain how payers will structure access. One possibility is that payers will continue sequencing requirements, positioning oveporexton after branded oxybates within step-therapy frameworks. Alternatively, coverage policies may instead support complementary use of oveporexton alongside oxybate therapies, reflecting their distinct roles in the sleep-wake cycle. Clinical opinion suggests the second option: that Xyrem and Xywav and oveporexton may not be substitutes, but rather complementary therapies that address different ends of the sleep-wake cycle. Xyrem and Xywav are expected to remain foundational for managing DNS due to their proven ability to consolidate sleep architecture.[1,2] In contrast, oveporexton, as a selective orexin 2 receptor agonist, is designed to restore daytime wakefulness but has not demonstrated an effect on disrupted nighttime sleep in narcolepsy. In either scenario, Xyrem and Xywav are expected to provide distinct nighttime-related therapeutic effects not contributed by treatment with oveporexton and should not be considered directly comparable.

Methodological Challenges. Comparing oveporexton to Xyrem or Xywav is further complicated by methodological differences in their respective pivotal trials. For oveporexton, the Maintenance of Wakefulness Test (MWT) is the primary endpoint, directly measuring the drug's intended effect of restoring objective daytime wakefulness.[4,9] In contrast, the pivotal trials for Xyrem and Xywav have relied on endpoints such as the Epworth Sleepiness Scale (ESS), which reflects subjective sleepiness, and frequency of cataplexy attacks.[1,2] Notably, only the pivotal Xyrem trial (2005) included MWT as a secondary endpoint; the Xywav pivotal trial did not include MWT at all. When the primary intervention of interest is evaluated using MWT, any comparator in ICER's comparative clinical and cost-effectiveness analyses should be assessed using the same primary endpoint to ensure methodological rigor and meaningful comparison.

Another critical methodological challenge in comparing oveporexton and Xyrem and Xywav are the differences in trial designs. The pivotal Xywav trial permitted participants to remain on stable doses of stimulants or wake-promoting agents throughout the study. Following a stabilization phase, participants were randomized to either continue Xywav or switch to placebo for a blinded withdrawal period.[10,11] In contrast, the oveporexton pivotal trial required complete washout of all concomitant sleep medications prior to enrollment, resulting in a placebo group with no background therapy.[4,9] These design distinctions introduce fundamental differences in how treatment effects were assessed across trials. Any comparative assessment must account for these factors, as they can influence efficacy outcomes and the generalizability of trial results to real-world practice.

Xyrem and Xywav Should Not Be Grouped as a Single Comparator

Despite the above-mentioned limitations, if Xyrem and Xywav are included as comparators, they should not be grouped together as a single comparator with Lumryz and/or other generic oxybates given the substantial differences among the products.

Sodium Burden. Xyrem is a sodium oxybate formulation, whereas Xywav is a mixed-cation oxybate in which sodium content is reduced by approximately 92% at equivalent doses. This distinction has tangible clinical implications: at the maximum recommended dose (9 g/night), Xyrem adds about 1,638 mg of sodium per day compared with ~130 mg of sodium for Xywav.[12-14] In narcolepsy patients, even in those under 25 years of age,[19] excess sodium intake increases hypertension and cardiovascular (CV) disease risk, including coronary events and stroke.[15-18] Given these established associations, chronic excess sodium exposure may influence long-term outcomes among patients with narcolepsy.[20-22] Reflecting this evidence, the US Food and Drug Administration determined that Xywav is clinically superior to high-sodium oxybate (Xyrem) due to its greater CV safety, as the reduction in sodium at recommended doses is expected to help a substantial portion of patients reduce their long-term risk of developing CV disease.[23] Hence, grouping Xywav with Xyrem and other sodium oxybates into a single comparator would overlook a key clinical distinction for Xywav with potential implications for whole-person health.

Individualized Therapy. In practice, clinicians tailor therapy based on patient-specific factors such as comorbidities, reproductive planning, and treatment goals. The American Academy of Sleep Medicine guideline underscores this individualized, symptom-targeted approach, in which therapies are selected to address specific manifestations such as EDS, cataplexy, or DNS.[24] Further, real-world evidence shows that clinicians routinely adjust dosing schedules to accommodate lifestyle factors and sleep patterns, with most identifying dosing flexibility as central to patient care.[25] Grouping these therapies into a single comparator would overlook these meaningful clinical distinctions and fail to reflect real-world prescribing practices.

Conclusion

In summary, a meaningful comparison of therapies for narcolepsy must account for important mechanistic, clinical, and methodological differences. Ultimately, comparator selection should reflect the pharmacologic and clinical realities of each therapy and account for the freedom that physicians require to tailor treatments to individual patient needs. In addition to the potentially mechanistically complementary role of Xyrem/Xywav and orexin agonists, it is also important to recognize that the core value and benefits of narcolepsy medications cannot be adequately quantified in dollars or life-year terms. We encourage ICER to acknowledge broader patient-centered benefits and the limitations of conventional metrics in fully capturing the value of treatments for narcolepsy.

Jazz appreciates the opportunity to provide these comments and thanks ICER for its continued commitment to a transparent and methodologically rigorous assessment process.

Kind regards,
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