April 7, 2026

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

RE: Jazz response to the draft evidence report for ICER's assessment of oveporexton for the treatment of narcolepsy type 1

Dear ICER Team,

Jazz Pharmaceuticals, Inc. (Jazz) appreciates the opportunity to provide comments on the Institute for Clinical and Economic Review (ICER) draft evidence report evaluating oveporexton for the treatment of narcolepsy type 1 (NT1). Jazz is committed to advancing innovative therapies that improve outcomes for patients living with serious neurological conditions. As a global, patient-focused, science-driven biopharmaceutical company, Jazz has built a leading neuroscience portfolio with a longstanding focus on sleep disorders.

In NT1, Jazz brings more than two decades of experience in sleep medicine, with approved therapies including Xyrem® and Xywav® that address the 24-hour, multi-symptom burden of disease. These treatments target key symptoms such as excessive daytime sleepiness (EDS) and cataplexy, while also improving overall disease symptoms and specific symptoms such as disrupted nighttime sleep, sleep quality, sleep paralysis, sleep-related hallucinations, patient functioning, and morning functioning.[1,2] Our research integrates both clinically validated endpoints and real-world patient experience, reflecting a commitment to generating evidence that is both rigorous and meaningful for patient care.

We appreciate ICER's characterization of NT1 and the consideration of prior comments reflected in the draft report. To further support a clinically relevant and methodologically robust assessment, Jazz offers the following observations on key modeling assumptions, treatment considerations, and sources of uncertainty that may influence the interpretation of cost-effectiveness results.

Focus the Analysis on High Sodium Oxybates to Ensure Validity of Model Inputs

ICER's draft report groups oxybate products as a single class and includes both high sodium oxybates (Xyrem, Lumryz, generic variants) and low sodium oxybate (Xywav) within this grouping. The inclusion of low sodium oxybate is not appropriate, as it is a distinct formulation with a safety profile that differs from high-sodium oxybate formulations. Low sodium oxybate is a mixed-cation (calcium, magnesium, potassium, and sodium) oxybate with approximately 92% lower sodium content than high-sodium oxybate at equivalent doses.[3,4] At the maximum Food and Drug Administration (FDA)-approved dose (9 g/night), this corresponds to approximately 1,600 mg (70% of the recommended daily amount) of daily sodium exposure with high-sodium

oxybate compared to ~130 mg (6% of the recommended daily amount) with low sodium oxybate.[3-5]

This difference has clear clinical relevance. There is well-established global consensus that prolonged excess sodium intake is associated with increased blood pressure and cardiovascular risk, including coronary events and stroke.[6-9] Given that NT1 requires chronic, often lifelong treatment, cumulative sodium exposure is an important consideration for long-term patient outcomes.[10-12] Reflecting this, the FDA determined that low sodium oxybate is clinically superior to high-sodium oxybate due to its reduced sodium content and associated reduction in cardiovascular risk.[13]

By grouping different oxybates, ICER introduces significant uncertainty by combining data across heterogenous oxybate formulations and evidence sources. Efficacy inputs are derived from multiple trials of oxybates, while discontinuation rates are sourced from a combination of trial-based estimates and long-term extension studies across different formulations. In addition, utility inputs are derived from multiple preference-based measures, including a mix of directly observed and mapped estimates across instruments. As documented in the literature and in ICER's limitations section, these approaches capture different dimensions and may respond differently to clinical change, which may introduce additional uncertainty into the model.[14-17] As a result, treatment benefit and treatment persistence may not be fully aligned to a common evidence base.

The underlying studies differ in patient populations, including variation in disease subtype and baseline severity, as well as in study design, duration, and use of concomitant therapies. We appreciate that ICER also acknowledges these differences and the resulting uncertainty, noting that variation in trial protocols, baseline characteristics, and treatment context may affect comparability across treatments. These sources of heterogeneity may not be fully captured when combining inputs across evidence sources, which could contribute to additional uncertainty in the model.

Combining different oxybates may not fully capture clinically meaningful differences in safety and could introduce additional complexity, given that discontinuation is the primary pathway through which adverse events influence model outcomes. In addition, inputs are drawn from multiple sources across different oxybate formulations, with limited data specific to low sodium oxybate, which may limit the model's ability to reflect product-specific outcomes. Taken together, these factors may influence estimates of treatment value and contribute to uncertainty in the results. Moreover, this approach may not fully reflect clinical practice, where treatment decisions are made based on product-specific characteristics, including sodium content, tolerability, and patient comorbidities.

Given that a majority of the inputs in the model are sourced from high sodium oxybate studies, we recommend that ICER consider limiting the generalizability of the findings to high sodium oxybates.

An ESS-based Approach to Utilities May Improve Consistency and Reduce Cross-trial Differences

ICER's base case combines utilities derived from multiple preference-based measures (PBMs). This approach may introduce uncertainty, as different instruments capture different health dimensions and may respond differently to clinical change—an issue ICER also acknowledges.[14-17]

Importantly, while ICER's updated model structure—where health states are defined based on treatment phase and response status (e.g., ESS ≤10 vs. >10)—is a meaningful step forward, some differences may remain between how health states are defined and how corresponding utilities are measured.

A symptom-based utility framework resolves these issues. Under an ESS-based approach:

- Utilities are anchored to clinically meaningful disease severity categories,
- A consistent method is applied across all treatments, and
- Utility estimation is aligned with the clinical endpoint used to define response in the model.

Importantly, this approach is supported in the literature. Prior economic models in NT1 have linked ESS changes to utility, reflecting the central role of EDS in driving quality of life.[18] Health technology assessment bodies, including both the National Institute for Health and Care Excellence and Canada's Drug Agency, have also recognized the limitations of generic PBMs in this condition and have accepted approaches that directly reflect symptom burden.[19,20]

In ICER's scenario analysis, shifting to an ESS-based utility approach shifts the incremental cost-effectiveness ratio by approximately 171%, suggesting that results are highly sensitive to this assumption. In this context, the choice of utility approach in the base case may warrant further consideration. These concerns are especially pronounced in NT1, where EDS is a primary driver of disease burden and quality of life.

Consider Uncertainty and Evolving Market Dynamics in Sodium Oxybate Pricing

We appreciate that ICER revised the assumed price for generic sodium oxybate to better reflect real-world costs. That said, the current assumption of approximately $160,000 is based on a single point estimate and may not fully capture the evolving and heterogenous pricing landscape. Pricing for oxybate is expected to vary substantially across formulations, manufacturers, and contracting arrangements, particularly as the market continues to evolve.

Pricing is an important input in cost-effectiveness analyses and can meaningfully influence results. Reliance on a single point estimate, especially in a market undergoing change, may not fully reflect the range of plausible comparator costs. In addition, changes in market structure, including increased competition and potential differentiation across products, may lead to

variability in pricing over time rather than a uniform trajectory. This dynamic is well described in the literature, as generic entry is often associated with price erosion over time.[21,22]

Given this uncertainty, incorporating a broader range of pricing assumptions may help support more robust interpretation of results. To enhance transparency and decision relevance, ICER may consider including alternative sodium oxybate pricing scenarios and presenting results across a range of plausible values. Including sodium oxybate pricing as a key parameter in one-way sensitivity analyses may also help illustrate its impact on model outcomes.

Ensure Analyses Reflect Uncertainty Around Oveporexton Pricing, Including the Potential for Higher Launch Pricing

ICER's cost-effectiveness analysis relies on a placeholder price of $175,000 for oveporexton. Given that oveporexton has not yet launched, there remains uncertainty around its eventual price, which may differ from this placeholder value. Historically, newly launched mechanistically novel therapies that are first in class are often launched at a substantial premium to existing therapies.[23] Launch pricing is expected to be $200,000 or higher, underscoring the importance of evaluating a range of plausible price points.

To support robust interpretation of results, ICER may consider presenting findings across a range of pricing scenarios and highlighting the sensitivity of results to this key input. Including oveporexton pricing in one-way sensitivity analyses would further illustrate its impact on model outcomes. As additional information becomes available, ICER may also consider updating the analysis to reflect real-world pricing to ensure that conclusions remain decision relevant.

Characterize Uncertainty Around the $150,000 per Quality-Adjusted Life Year (QALY) Result

The proximity of the base case incremental cost-effectiveness ratio for oveporexton versus sodium oxybate to a commonly cited cost-effectiveness threshold highlights uncertainty in the model and may make interpretation of the results for voting purposes more challenging.

When an incremental cost-effectiveness ratio falls at or near a decision threshold, even modest changes in assumptions can shift results above or below that threshold. As a result, the interpretation of cost-effectiveness becomes highly sensitive to inputs, including those subject to uncertainty in the current model. These include assumptions related to utility estimation, comparator pricing, discontinuation, placeholder pricing, and the long-term durability of oveporexton, which remains uncertain given the relatively short duration of available clinical data. In this context, presenting a single point estimate that aligns with the cost-effectiveness threshold may overstate the certainty of the model and its conclusions.

To support more appropriate interpretation, ICER may consider:

- Emphasizing the uncertainty surrounding the base case incremental cost-effectiveness ratio, given its proximity to the $150,000 per QALY threshold, and

- Illustrating how variation in key inputs affects whether results fall above or below this threshold.

Highlighting this uncertainty could help ensure that decision-makers understand that conclusions regarding cost-effectiveness are contingent on assumptions that remain uncertain.

Conclusion

In summary, several key assumptions in the draft evidence report, including grouping oxybate formulations, integration of heterogeneous clinical inputs from multiple evidence sources, the use of utilities derived and applied inconsistently, and pricing inputs, introduce uncertainty and may affect the interpretation of the cost-effectiveness results. These issues are especially relevant given that the base case incremental cost-effectiveness ratio for oveporexton versus sodium oxybate falls at a commonly cited willingness-to-pay threshold, where conclusions are inherently sensitive to modeling choices.

We appreciate that ICER has made important updates to the model in response to prior feedback. As outlined in this letter, there remain areas where further refinement may strengthen the analysis. Addressing these considerations could support improved internal consistency, clinical validity, and transparency. Specifically, limiting the generalizability of the findings to high sodium oxybates, aligning utilities with symptom-based outcomes, and further characterizing uncertainty in pricing and key model inputs may help provide a more robust and decision-relevant assessment.

We appreciate ICER's continued efforts to incorporate stakeholder feedback and look forward to ongoing refinement of the model to ensure that conclusions reflect the available evidence and the clinical context of NT1 treatment.

Kind regards,
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April 7, 2026

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RE: Public comments to ICER's Draft Evidence Report for the assessment of the investigative compound* oveporexton for narcolepsy type 1

Dear ICER:

Takeda appreciates the opportunity to provide comment on the draft evidence report for ICER's evaluation of oveporexton in narcolepsy Type 1 (NT1). We thank ICER for its careful consideration of our previous concerns and for the resulting updates to the analysis.

As detailed in this letter, NT1 is a chronic, lifelong, multi-symptom, around-the-clock neurologic sleep-wake disorder characterized by a full spectrum of symptoms (including excessive daytime sleepiness [EDS] and cataplexy), and often accompanied by cognitive, mood, and automatic behaviors, which can severely affect day-to-day functioning and contribute to substantial burden and unmet need for patients and families.[1-6] ICER's assessment appropriately addresses several important considerations in this therapeutic space, including the use of treatment-specific, trial-based utilities in the base case (rather than ESS-specific utilities), application of a clinically appropriate ESS responder definition (ESS ≤10), an updated model framework that removes the "off-treatment" state that previously favored comparators with high discontinuation rates, and use of a consistent long-term discontinuation rate across treatments.

Building on this foundation, ICER's analysis could be further refined to better reflect the real-world disease burden and associated costs of NT1, including the full spectrum of symptoms, and the limitations of current therapies that meaningfully shape treatment patterns in clinical practice. To support a more comprehensive assessment, we expand on six topics below:

1. **"No treatment" is not an appropriate clinical comparator, but rather a real-world manifestation of unmet need and access/tolerability barriers**
2. **The consequences for poorly controlled disease are not fully captured**
3. **Xyrem, Xywav, and Lumryz are distinct products and are not substitutable**
4. **Dosing assumptions in the cost-effectiveness model do not reflect real-world use**
5. **Oveporexton data demonstrates that it has the potential to be a highly efficacious monotherapy treatment if FDA approved; there is no evidence indicating routine supplemental treatment is needed**
6. **The ESS severity–based utility scenario should be clearly caveated regarding applicability to the NT1 population**

*Oveporexton is presently in Phase 3 development for the treatment of narcolepsy type 1. Oveporexton is an investigational product for the treatment of narcolepsy type 1 that has not been approved by the US Food and Drug Administration (FDA). The safety and effectiveness of oveporexton have not been established.

Further detail on these key discussion points is provided below. Our comments address both the clinical and economic components of ICER's assessment.

1. **"No treatment" is not an appropriate clinical comparator, but rather a real-world manifestation of unmet need and access/tolerability barriers**

ICER evaluated the clinical efficacy and safety of oveporexton versus "no treatment", as represented by the placebo arms of the Phase 3 TAK-861-3001 and TAK-861-3002 trials.[7,8] While Takeda recognizes that anchoring the cost-effectiveness model on "no treatment" was a necessary statistical approach to provide a common comparator for indirect analyses, ICER's emphasis on conclusions that oveporexton is not cost-effective versus "no treatment" warrants additional context to avoid misinterpretation. Highlighting such results without clear caveats risks implying that "no treatment" is a clinically acceptable treatment strategy for NT1 and that patients can manage the substantial and persistent burden of NT1 symptoms without therapy.

We strongly encourage ICER to add explicit context clarifying that "no treatment" is not a guideline-concordant treatment option in NT1 and should not be interpreted as a normative comparator. In real-world settings, periods of untreated disease more likely reflect unmet need and systemic barriers (e.g., access, affordability, coverage restrictions, tolerability limitations, contraindications, discontinuation), rather than an evidence-based or ethical standard of care. Accordingly, "no treatment" should be presented as a limited real-world benchmark (i.e., a manifestation of gaps in care) rather than a guideline-aligned clinical alternative.

ICER should clarify that cost-effectiveness results versus "no treatment" may be sensitive to uncertain disease burden inputs and to limitations in translating trial endpoints into broader real-world benefits. In particular, incomplete capture of the full spectrum of NT1 symptoms and longer-term functional outcomes and disease-related harms (e.g., accident/injury risk, workplace safety, increased long-term risk of cardiovascular disease (CVD), and downstream mental health consequences) may lead the model to understate the impact patients experience with effective treatment. [2,9,10,11,12] For these reasons, conclusions drawn from a "no treatment" anchor should be clearly caveated, with greater emphasis placed on the fact "no treatment" is not an evidence-based or ethical standard of care.

2. **The consequences for poorly controlled disease are not fully captured**

ICER's model appears to limit the consequences of poorly controlled NT1 largely to productivity losses, modest incremental non-drug direct medical costs, and health-related quality-of-life (HRQoL) decrements. By design, the model does not incorporate potentially important lifetime downstream outcomes such as CVD, major adverse cardiovascular events (MACE), accidents/injuries, mental health comorbidities, and excess mortality due to gaps in evidence directly linking treatment to reductions in these outcomes.[2,9,10,11,12]

While we recognize the evidentiary challenges, excluding the costs, mortality, and HRQoL associated with infrequent but serious NT1 consequences systematically underestimates the burden of uncontrolled disease and therefore the value of effective treatment. This concern is supported by ICER's own QALY shortfall findings, which highlight the substantial unmet need and lifelong burden experienced by people with NT1.

In addition, direct costs related to healthcare resource use (HCRU) for uncontrolled NT1 are thought to be underestimated in the current framework, which creates minimal modeled disadvantage for untreated patients. This risks contradicting clinical practice and stakeholder expectations, where poorly controlled NT1 is associated with meaningful morbidity, safety risks, and broader societal and economic impacts that extend beyond what is typically captured in claims-based HCRU alone, including safety risks and downstream harms (e.g., motor vehicle accidents, other injuries, and suicidality) and potential excess mortality (e.g., ~40% higher risk reported in NT1/NT2 modeling).[10,12] In addition, the model does not readily capture the broader "life course" consequences of symptoms beginning early in life (including impacts on educational and professional attainment and loss of independence), caregiver burden and out-of-pocket costs, or cognitive impairment and psychosocial impacts frequently reported by patients and families.

ICER should therefore consider adding explicit context that cost-effectiveness results may not capture the full burden of NT1, including the full spectrum of NT1 symptoms and potential longer-term benefits conferred by effective treatment, and that the clinical and utility inputs underpinning the model may not fully reflect the benefits experienced by patients. At a minimum, ICER should clearly characterize these omissions as limitations that may bias results against treatments that improve multi-domain symptoms and functioning.

3. Xyrem, Xywav, and Lumryz are distinct products and are not substitutable

ICER's analysis groups different oxybate formulations (Xyrem and generics, Xywav, and Lumryz) into a single treatment category, assuming comparable efficacy, pooling discontinuation rates, and applying the cost of generic sodium oxybate as a class-level proxy in the reference case. However, these products are not therapeutically equivalent or substitutable, as evidenced by the fact that they are not designated as therapeutically equivalent in the FDA Orange Book.[13,14,15,16]

While ICER acknowledges that product-specific differences are not fully captured in their analysis, we have several concerns about how this approach limits the real-world relevance. First, oxybate formulations differ in clinical efficacy, side effects and tolerability, which may meaningfully influence adherence, persistence, and HRQoL. For example, nausea, dizziness, and vomiting are reported across formulations (≥5% in clinical trial participants), but lower-sodium oxybate is more often associated with loss of appetite, anxiety, and diarrhea.[17-21] Differences in taste/texture,[22] once- vs. twice-nightly dosing,[23] and pharmacokinetic profiles may also affect compliance, effectiveness, and lifestyle.

Furthermore, using generic sodium oxybate as a cost proxy for the entire class understates real-world treatment costs, as only Xyrem has an authorized generic;[17,20,21] Xywav and Lumryz, neither of which has a generic alternative,[18,19] represent a large and growing share of oxybate use,[24,25,26] and payers do not treat these products as interchangeable but instead make formulation-specific coverage decisions based on distinct clinical and cost profiles.

Taken together, this aggregation obscures real differences that matter in practice and ultimately limits the ability of stakeholders to draw clinically relevant conclusions from the ICER analysis.

4. **Dosing assumptions in the cost-effectiveness model may not reflect real-world use**

In the current cost-effectiveness model, ICER's pricing assumptions for key comparators do not fully reflect real-world use. Real-world dosing patterns for pitolisant and sodium oxybates suggest a greater proportion of patients use higher doses than those currently modeled to achieve the desired treatment effect.[24] Understating real-world dosing patterns can underestimate comparator costs and, in turn, influence incremental cost-effectiveness results. To better align the analysis with clinical practice, Takeda recommends that ICER estimate comparator drug costs using a weighted average that reflects observed real-world dosing across the distinct drug products.

5. **Oveporexton data demonstrates that it has the potential to be a highly efficacious monotherapy treatment if FDA approved; there is no evidence indicating routine supplemental treatment is needed**

One of the key uncertainties ICER raises is whether oveporexton will be used in combination with other treatments in real-world practice. While it is true that current NT1 management often involves multiple medications, ICER should avoid implying that oveporexton will likely require add-on therapy to achieve adequate symptom control.

Importantly, the reason combination therapy is common today is that available options are largely symptom-directed and often address only a subset of the spectrum of NT1 symptoms, necessitating multi-drug regimens, as well as possible switching and dose adjustments to balance incomplete efficacy and tolerability.[27] Oveporexton is meaningfully different: with a novel mechanism of action aimed at the underlying cause of NT1.[28,29,30] In clinical trials it has demonstrated robust and durable efficacy as a monotherapy across multiple symptom domains.[7,8] In a dose-blinded Phase 2 study, data showed no discontinuations due to loss of efficacy at 6 months,[31] and Phase 3 data indicates that approximately 84% of patients achieved normal ESS scores (no EDS) on oveporexton monotherapy.[7,8] In addition, oveporexton monotherapy substantially improved hallucinations or sleep paralysis in ~85% of Phase 3 participants, and 67% of patients experienced meaningful improvement in disturbed nighttime sleep.[32] Taken together, these results suggest that oveporexton monotherapy has the potential to reduce, not increase, the need for multi-drug symptom-directed regimens in NT1 and its real-world use should be based on joint patient and clinician decision making.

Currently, the efficacy and safety of oveporexton in combination with other drugs requires further study. As such, strong inferences about routine combination use introduce unnecessary uncertainty and risk conflating two distinct concepts: (1) background real-world polypharmacy driven by the limitations of existing symptom-directed therapies, and (2) a clinical need for add-on therapy because oveporexton may be insufficient on its own. There is no evidence or expert consensus indicating that oveporexton would require supplemental treatment for optimal symptom control.

Assuming that oveporexton will "likely" require combination therapy based primarily on experience with therapies that treat individual symptoms risks mischaracterizing the clinical evidence to date and understating the potential for oveporexton to simplify treatment in NT1. ICER should therefore consider reassessing its assumptions and more carefully qualify statements regarding likely combination use.

6. **The ESS severity–based utility scenario should be clearly caveated regarding applicability to the NT1 population**

We would also like to note ICER's scenario analysis applying utilities mapped from ESS severity to isolate the impact of EDS on quality of life. ESS severity–based utilities should be interpreted cautiously in NT1. NT1 burden extends beyond EDS,[33] and oveporexton's potential treatment benefits may not be fully reflected when utility is driven solely by ESS. In addition, the ESS-based utility estimates used in this scenario were elicited largely from an obstructive sleep apnea population, which may limit applicability to people with NT1.[34] ICER should explicitly qualify this scenario analysis with these limitations and avoid over-weighting its results relative to the base case using oveporexton trial-based utilities.

Thank you for the opportunity to comment on the Draft Evidence Report for the assessment of oveporexton for NT1. In light of the considerations outlined above, we encourage ICER to reassess its approach and assumptions to ensure the analysis better reflects the broader real-world burden and costs of NT1 and the real-world constraints of current therapies that drive treatment patterns. If you have any questions, please feel free to reach out.

Best regards,

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