



**Institute for
Patient Access**

December 4, 2019

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Comments on ICER's Draft Evidence Report: Acute Treatment for Migraine

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide input regarding ICER's "Draft Evidence Report: Acute Treatment for Migraine."

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality health care. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient access to approved therapies and appropriate clinical care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of physicians committed to shaping a patient-centered health care system. IfPA is a 501(c)(3) public charity nonprofit organization.

IfPA Comments on ICER's Draft Evidence Report

The draft evidence report encompasses three medicines designed to provide "acute treatment" for migraine patients – ubrogepant, rimegepant and lasmiditan. There were two populations of interest for this evaluation:

- Patients whose acute migraine episodes have not responded well to non-prescription medications; and,
- Patients whose acute migraine episodes have not responded well to non-prescription medications and for whom triptans have not been effective, are not well tolerated, or are contraindicated.

Further, the analysis evaluated patients who were 18 years of age and older, and whose migraine symptoms were not chronic (fewer than 15 headache days per month).

The report suffers from three deficiencies that have a material impact on the estimated value of the medicines. These deficiencies include:

- Failure to incorporate the benefits of reduced comorbidities that better migraine management enables;
- Methodological errors that undermine the evaluation results; and
- Inappropriate or overly restrictive assumptions regarding the medicines' efficacy.

Failure to Incorporate the Benefits of Reduced Comorbidities

Section 1.4 of the report, “Insights Gained from Discussions with Patients and Patient Groups,” documents the devastating impact of migraine attacks, including the connection between migraine and higher risks for other illnesses. These other illnesses include stroke, coronary heart disease, hypertension, depression, anxiety, epilepsy and asthma.¹ These comorbid conditions create additional health care and economic costs that are linked to migraine.

More effective migraine treatments help patients better manage these comorbid conditions. In fact, effective treatment of migraine early on, when patients' pain is at a lower intensity, yields significant health benefits and is an important predictor of improved outcomes.² The additional benefits will include better patient health outcomes, reduced economic costs on patients and their caregivers, and lower overall health care costs.

Consequently, ubrogepant, rimegepant and lasmiditan will provide value by lowering the costs associated with comorbid conditions in addition to the value of reducing the direct costs associated with migraine. While acknowledging that these comorbidities exist, the report does not attempt to estimate the value of potentially reducing these comorbidities.

Since the report does not quantify the benefits of reduced comorbidities, the results, by definition, underestimate the benefits patients receive from these treatments. Unless the report corrects this error and accounts for the full benefits of effective migraine treatment, ICER's analysis will be an unreliable guide for valuating the medicines.

Methodological Errors

On page 23, the report states that ICER “conducted network meta-analyses (NMAs) for each outcome of interest.” According to page 24 of the report, however, ICER identified “only one head-to-head trial of one of the interventions versus a comparator of interest (rimegepant vs sumatriptan).”

Using an NMA analysis when only one head-to-head study has been identified is methodologically problematic. According to a 2019 study in the *Journal of Clinical Epidemiology*, network meta-analyses improved the precision of results only when at least two head-to-head studies are available. The precision of the results actually worsened when only one head-to-head study was available.³ Citing from the study's abstract:

¹ Wang SJ, Chen PK, and Fuh JL (2010) “Comorbidities of Migraine” *Frontiers in Neurology* 1:16 August 23; <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3008936/>.

² Valade D (2009) “Early treatment of acute migraine: New evidence of benefits” *Cephalalgia*, December 1; <https://journals.sagepub.com/doi/abs/10.1177/03331024090290S304>.

³ Lin L, Xing A, Kofler MJ, and Murad MH (2019) “Borrowing of strength from indirect evidence in 40 network meta-analyses” *Journal of Clinical Epidemiology*, Feb; 106; 41-49; <https://www.ncbi.nlm.nih.gov/pubmed/30342086>.

Although NMAs have the potential to provide more precise results than those only based on direct evidence, the incremental gain may reliably occur only when at least two head-to-head studies are available, and treatments are well connected. Researchers should routinely report and compare the results from both network and pairwise meta-analyses.

Further, as outlined in Temple University's guide to network meta-analyses, NMAs are an evolving method that is subject to strict limitations.⁴ It does not appear that the cost-effectiveness evaluation accounted for these limitations to ensure that the results are strengthened, not weakened, by the use of the NMA methodology.

Another concern is that the report compares modern studies for ubrogepant, rimegepant, and lasmiditan to triptan clinical studies that were conducted one-to-two decades ago. It is possible that material differences have arisen over time that make the comparison of studies from today to studies conducted up to two decades ago inappropriate. Consequently, the report needs to justify why it is appropriate to compare studies that were conducted up to two decades apart. Without such a justification, there are serious concerns regarding the accuracy of the results.

Questionable Assumptions That Create a Lower-Value Bias

Ubrogepant, rimegepant and lasmiditan are novel treatments, and as a result, the clinical data regarding these medicines are limited. The desire to perform cost-effectiveness analyses prior to a medicine's availability to patients is understandable – it allows ICER to suggest a price for the medicine before patients and insurance companies must pay for the medicine. But this timing introduces an unacceptable level of uncertainty into the report and necessitates ICER to make questionable assumptions that introduce unknown errors.

Overly Restrictive Pain Relief Assumptions

As documented on page 23 of the report, “the primary efficacy endpoint in all trials was freedom from pain at two hours after treatment.” This narrow definition of efficacy is problematic.

For instance, two phase-III clinical trials for rimegepant administered as a 75 mg oral dose found that 19.2% and 19.6% of patients achieved freedom from pain by two hours, (compared to 14.2% and 12% for the placebo group). But, importantly, the percentage of patients who were pain free increased over time; 66% of patients were pain free by eight hours compared to 47% for the placebo group.⁵ This increase in the number of patients helped at eight hours means that limiting the benefits to a two-hour period has likely resulted in an undervalued estimate of the benefit of these medicines to patients with migraine.

Another troubling assumption regarding pain arises because the report classifies pain into three levels: mild, moderate and severe. It is commonly understood that helping patients with migraine experience requires a much more sophisticated understanding of the type of pains they are experiencing. As just one example, patients living with migraine aura often experience the

⁴ <https://guides.temple.edu/c.php?g=78618&p=4156609>.

⁵ Thien Phu D, Song G, Messoud (2019) “Therapeutic novelties in migraine: new drugs, new hope?” *The Journal of Headache and Pain*, 20 April 17; <https://thejournalofheadacheandpain.biomedcentral.com/articles/10.1186/s10194-019-0974-3>.

sensitivity to light and sound differently. These differences must be considered in order to effectively control a patient's migraine attack. It is not possible to account for these differences, however, when a clinical effectiveness model oversimplifies a patient's pain experience into a linear "mild-moderate-severe" categorization.

Ignoring the Potential Benefits of Migraine Prevention

According to page 44 of the report, ICER "do[es] not feel that current evidence supports a conclusion that treatment with lasmiditan, rimegepant or ubrogepant decreases migraine frequency over time." However, this assumption is based on the limitations of current studies, not based on a finding that these medicines have no impact on migraine frequency.

In fact, there is growing evidence that the "gepant" class may have benefits with respect to migraine prevention. For example, atogepant, "an oral small-molecule migraine drug...showed safety and efficacy for preventing migraine headaches in a phase 2/3, dose-ranging trial with 825 evaluable patients."⁶ The benefits for patients from a medicine that can prevent migraine headaches are potentially substantial, and it is troubling to assume that this benefit does not exist when the latest medical evidence indicates that the gepant drug class may actually provide these benefits. Further, this represents another instance where the report's assumptions bias the results toward a finding that the medicines have less value.

A Narrow Definition of Value

In Section 4.2, the methods section, the report states that the base case analysis was based only on direct U.S. health care costs. Patients living with migraine face many other costs, however. The annual quantifiable indirect economic costs alone, mostly from lost productivity and missed work, have been estimated at \$2,350 per patient. Further, these costs do not include the value of being in less pain, or the value gained by having a greater ability to participate in more personally fulfilling activities. The assumption that these meaningful benefits are not worth including is another instance where the report's assumptions undervalue the benefits to migraine patients from a more effective treatment.

The Report's Assumed Utility Scores

The chosen utility/disutility measures are important assumptions that attempt to quantify how much patients value an effective treatment and meaningfully impact the results. Page 65 of the report states that "disutilities of -0.5 were assumed for those patients who were hospitalized or required an ED visit. Hospitalizations were assumed to last for 2 days, ED visits for 1 day. We did not include a disutility score for patients suffering from nausea and/or vomiting, photophobia, or phonophobia due to lack of data."

As this quote indicates, the report's chosen elasticities are predicated on several questionable assumptions that bias the results toward undervaluing the medicines. First, the assumptions of what to include in the utility/disutility scores are essential. Since the report "did not include a disutility score for patients suffering from nausea and/or vomiting, photophobia, or

⁶ Zoler ML (2019) "Atogepant shows safety, efficacy for migraine prevention" *MDEdge: Neurology* July 25; <https://www.mdedge.com/neurology/article/205295/headache-migraine/atogepant-shows-safety-efficacy-migraine-prevention>.

phonophobia”, the benefits from treatments that reduce these conditions are, by definition, ignored in the report.

Second, the assumed utility values were based on a small number of studies. With such a small number of studies used to justify these crucial assumptions, it is highly questionable that the chosen values accurately represent the utility/disutility of the average patient living with migraine.

Finally, it is not possible for one average utility score to be applicable to all individual patients, even if it were representative of the population as a whole. Therefore, the value findings from the report are not representative of how much any individual patient will value a more effective treatment.

Conclusion

Migraine is a disabling condition for far too many Americans. Effective migraine control can meaningfully improve the quality of life for patients living with this disease, and can also provide offsetting health care savings. It is imperative that the any cost-effectiveness evaluation accounts for the full benefits enabled by medicines that offer effective migraine control.

Yet the methodology employed by the draft evidence report undervalues the benefits of a more effective migraine treatment, commits methodological errors and relies on questionable assumptions. ICER should consider comprehensive changes to its approach and methodology before finalizing the study. Without these changes, the report’s findings cannot be relied upon as an accurate assessment of the medicines’ value.

Thank you for the opportunity to provide comments on these important issues. Please contact us should you have any questions, or would like us to provide further comments, at 202-499-4114.

Sincerely,



Brian Kennedy
Executive Director