Acute Treatments for Migraine: Final Policy Recommendations

February 25, 2020

Policy Recommendations

Introduction

Following its deliberation on the evidence, the Midwest CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on the use of lasmiditan, ubrogepant, and rimegepant for acute treatment of migraine. The policy roundtable members included two patient advocates, two clinical experts, two payers, and three representatives from pharmaceutical manufacturers. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants. All Policy Roundtable participants and conflict of interest disclosures for all meeting participants can be found in the Appendix of this document. A recording of the conversation can be accessed here, immediately following the voting portion of the meeting.

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Payers

(1) Given that the evidence does not demonstrate superiority of the newer agents to existing less-expensive treatment options, it is reasonable for insurers and other payers to develop prior authorization criteria for lasmiditan, rimegepant and ubrogepant to ensure prudent use of these new therapies.

(2) For ubrogepant and rimegepant, given their similar mechanisms of action and available evidence suggesting no major differences in safety or effectiveness, it is not unreasonable for payers to negotiate lower prices by offering preferential formulary status to one or the other drug, including the possibility of exclusion of one of the drugs. If only one drug is covered, however, clinicians and patients should have the ability to appeal for coverage for the other gepant drug should a trial of the favored drug not produce adequate success.

(3) Prior authorization criteria should be based on clinical evidence, specialty society guidelines, and input from clinical experts and patient groups. The process for authorization should be clear and efficient for providers. Options for specific elements of coverage criteria within insurance coverage policies are discussed below.

Ubrogepant and Rimegepant

Patient Eligibility Criteria

a. **Patient population:** The Food and Drug Administration (FDA) indication for ubrogepant includes acute treatment of all adults with migraine, with or without aura. We anticipate the same broad language will be used should rimegepant be approved. Clinical trials for both agents included a narrower spectrum of adults: patients generally had a long history of migraine with a high frequency and intensity of symptoms. On average, over 80% were female, with an average age of 40 years, having had migraines for approximately 20 years, with 3-5 migraine attacks per month of a moderate (70%) or severe (30%) intensity. About 20-25% of trial participants were receiving medications to prevent migraine attacks. Clinical experts and patient advocates suggest that although the clinical trial populations were more severely affected, on average, than all patients with migraine, there is no evidence-based reason to try to limit coverage based on some metric of severity such as number of migraines per month. Prior use of triptans as a coverage consideration is discussed below.

b. **Diagnosis**: Clinician attestation of migraine diagnosis is reasonable since there are no specific diagnostic tests.

c. **Ineligible for triptans, intolerance of triptans, or inadequate response to triptans:** Given that the evidence of response to these newer agents does not suggest they are superior to triptans, clinical experts, patient advocates, and manufacturers agreed that requiring patients to try triptans first before receiving coverage for the newer agents is reasonable if patients are clinically eligible. Clinical experts highlighted that triptans are under-prescribed, and some patients have not tried triptans due to concerns about side effects or concerns about vasoconstriction in those not at high risk for cardiovascular disease. Some patients will have tried triptans in the past and had intolerable side effects. Attestation of clinical ineligibility or intolerance was favored by clinical experts and patient advocates over formal medical record documentation given the long-term nature of migraine and the difficulty of finding past medical records to document CV events or prior side effects.

   For patients who are eligible to try triptans, there is no evidence-based basis for a threshold number of different triptans that should be tried to determine whether adequate treatment is achieved. Clinical experts and patient advocates acknowledge that many patients find adequate relief with one triptan even after finding other triptans inadequate. The likelihood of finding a triptan that works does diminish after each trial, however, so a requirement of trying 1-2 triptans was viewed as reasonable whereas requiring more was viewed as less reasonable. Trying to devise a metric for “inadequate” response by looking at rescue medication use or other factors was not viewed as clinically reasonable.

Provider Criteria

Specialist prescribing requirement: Triptans were originally a specialty-only prescription in many health systems but soon after launch prescribing was broadened to all primary care clinicians. Given that ubrogepant and rimegepant seem to have a benign safety profile it seems reasonable to allow primary care prescribing at launch, although some payers may wish to require consultation with a specialist to ensure that the diagnosis of migraine is being adequately made and that trials of triptans are maximized before consideration of these newer agents.

Renewal criteria

Because patients will have the best sense of whether the treatment is proving successful, it does not seem that requiring attestation from clinicians of clinical benefit before renewing prescriptions will be helpful in achieving appropriate use.

Concurrent Medications

There is no evidence available with which to judge the safety or effectiveness of use of these new agents in conjunction with concomitant triptan use. Clinical experts suggested that concomitant use would be desired by some/many patients but acknowledged the lack of evidence to support this strategy. Given that payers are likely to reserve coverage of these newer agents to patients who have not had adequate relief from triptans, some may consider setting initial coverage conditions that exclude concomitant use, at least until further data become available, but it may also be reasonable to provide coverage for one or more triptans and one of the newer agents.

Quantity Limits

Payers have used limits on the number of triptan pills dispensed per month as a means of reducing the risk of medication overuse headache (MOH). Similar quantity limits could be considered by payers for these new medications. Given that these medications have a different mechanism of action it is unknown whether they will also have the potential to cause MOH. Clinical experts cited the positive clinical experience to date with preventive CGRP medications and were therefore hopeful that gepant acute treatments would not cause MOH, but experts were also aware that triptans themselves were touted as being free of this concern when they were first launched. In general, clinical experts and patient advocates felt that quantity limits would not promote positive outcomes but acknowledged the likelihood that payers would consider quantity limits until longer-term data on MOH were available. Clinical experts also advised that payers should reconsider their quantity limits on triptans. If triptans are working well for patients but the quantity limits leave gaps in treatment, it will be natural for patients to seek other options, such as the gepants or lasmiditan. Loosening quantity limits for triptans may therefore be better clinically for patients as well as ultimately more cost-effective for payers.

Lasmiditan

Patient Eligibility Criteria

a. **Patient population:** The Food and Drug Administration (FDA) indication for lasmiditan includes acute treatment of all adults with migraine, with or without aura. Clinical trials for lasmiditan included a narrower spectrum of adult: patients generally had a long history of migraine with a high frequency and intensity of symptoms. On average, over 80% were female, with an average age of approximately 40 years, having had migraines for 15-20 years, with 3-5 migraine attacks per month of a moderate (approximately 70%) or severe (approximately 30%) intensity, and about 20-25% were receiving medications to prevent migraine attacks. Clinical experts and patient advocates suggest that although the clinical trial populations were more severely affected, on average, than all patients with migraine, there is no evidence-based reason to try to limit coverage based on some metric of severity such as number of migraines per month.

   Because the mechanism of action of lasmiditan has some similarities to that of triptans, some payers may wonder whether there should be any CV restrictions. Clinical trials excluded patients with known coronary artery disease; clinically significant arrythmia; uncontrolled hypertension; or conditions increasing the risk of seizures. The FDA, however, put no restrictions on the label, and clinical experts advised that except for clear evidence of major CAD they did not believe there were reasons to consider lasmiditan an inappropriate treatment option. Unlike triptans, lasmiditan does not cause vasoconstriction.

b. **Diagnosis**: Clinician attestation of migraine diagnosis is reasonable since there are no specific diagnostic tests.

c. **Ineligible for triptans or inadequate response to triptans:** Given that the evidence of response to lasmiditan does not suggest it is superior to triptans, clinical experts, patient advocates, and manufacturers agreed that requiring patients to try triptans first before receiving coverage is reasonable if patients are clinically eligible. Clinical experts highlighted that triptans are under-prescribed, and some patients have not tried triptans due to concerns about side effects or concerns about vasoconstriction in those who not at high risk for cardiovascular disease. Attestation of clinical ineligibility was still favored over formal medical record documentation given the long-term nature of migraine and the difficulty of finding past medical records to document CV events that would make a patient ineligible.

   For patients who are eligible to try triptans, there is no evidence-based basis for a threshold number of different triptans that should be tried to determine whether adequate treatment is achieved. Clinical experts and patient advocates acknowledge that many patients find adequate relief with one triptan even after finding other triptans inadequate. The likelihood of finding a triptan that works does diminish after each trial, however, so a requirement of trying 1-2 triptans was viewed as reasonable whereas requiring more was viewed as less reasonable. Trying to devise a metric for "inadequate" response by looking at rescue

medication use or other factors was not viewed as clinically reasonable.

Provider Criteria

Specialist prescribing requirement: Triptans were originally a specialty-only prescription in many health systems but very soon prescribing was broadened to all primary care clinicians. Given that lasmiditan seems to have a benign safety profile and may have less risk of vasoconstriction than the triptans, it does seems reasonable to allow primary care prescribing at launch, although some payers may wish to require consultation with a specialist to ensure that the diagnosis of migraine is being adequately made and that trials of triptans are maximized before consideration of these newer agents. This may be more likely for lasmiditan than for the gepants given the FDA warning about driving within 8 hours of taking lasmiditan.

Renewal criteria

Because patients will have the best sense of whether the treatment is proving successful, it does not seem that requiring attestation from clinicians of clinical benefit before renewing prescriptions will be helpful in achieving appropriate use.

Concurrent Medications

There is no evidence available with which to judge the safety or effectiveness of use of lasmiditan in conjunction with concomitant triptan or gepant use. Clinical experts suggested that concomitant use would be desired by some/many patients but acknowledged the lack of evidence to support this strategy. Given that the mechanism of action for lasmiditan affects the same pathway as triptans it would seem to be more reasonable to limit coverage to one or the other. Coverage for simultaneous gepant and lasmiditan use at this time does not seem likely given that all agents are new to practice and there are no data on concomitant use. As the safety profiles of the drugs become more established, payers should consider whether requests for concomitant use appear more reasonable.

Quantity Limits

Payers have used limits on the number of triptan pills dispensed per month as a means of reducing the risk of medication overuse headache (MOH). Similar quantity limits are very likely to be considered by payers for lasmiditan. Given that lasmiditan is thought to have a similar mechanism of action, it is possible that it will also have the potential to cause MOH. In general, clinical experts and patient advocates acknowledged the likelihood that payers would consider quantity limits until longer-term data on MOH were available. Clinical experts also advised that payers should reconsider their quantity limits on triptans. If triptans are working well for patients but the quantity limits leave gaps in treatment, it will be natural for patients to seek other options, such as the gepants or lasmiditan. Loosening quantity limits for triptans may therefore be better clinically for patients as well as ultimately more cost-effective for payers.

Providers

(1) With the advent of these new treatment options, specialists in migraine treatment should seek new avenues to educate primary care clinicians on the appropriate use of triptans and other acute treatment options in order to maximize the appropriate care of the substantial population of patients with migraine while helping to control costs.

During the roundtable discussion, experts in migraine treatment described how triptans are often under-prescribed for acute treatment of migraine because of clinician concerns about potential risks, most prominently vasoconstriction. Triptans have been used for over 20 years and the evidence for clinically important vasoconstriction is very limited. Though this may be due to the cautious use of this class of medications in individuals at high risk for cardiovascular disease, it is more likely that the actual risks of these medications are lower than some clinicians may think. Migraine specialists should therefore work through their specialty societies and through their own care delivery systems to develop educational content for primary care and emergency medicine clinicians to help dispel old ideas about existing therapies and provide guidance on how best to incorporate new medications into clinical practice.

(2) Migraine specialists and specialty societies should update guideline recommendations to address the role of these new medications for acute treatments for migraine.

The availability of new medications for acute treatment of migraine with novel mechanisms of action point to a potentially major change in clinical practice. Patients and experts highlighted that that the large number of individuals with migraine in whom these new medications may be considered mean that it will not be practical to require specialist assessment and care of all eligible patients. In order to ensure clinicians have up to date information about the role of these new medications, it is incumbent on professional societies to develop and update clinical practice guidelines, especially in the setting of potentially major changes in available therapies. Placing these new agents into practice and helping clinicians identify their role in a rapidly changing landscape is critical to ensuring clinicians have the knowledge to wisely use these new therapies. A key aspect of these efforts is to ensure that guidelines are developed using rigorous methods that include input from a range of experts, primary care clinicians and patients with the condition, as well as explicit disclosure and monitoring of potential conflicts of interest.

Manufacturers and Researchers

(1) Manufacturers and researchers should develop long term comparative trials of acute treatments for migraine that assess outcomes over the entire course of a migraine attack.

Comments during the policy roundtable highlighted some of the important research gaps that limit identifying the best treatment for an individual patient. Though the choice of assessing primary outcomes at two hours was recognized to be arbitrary, it limits the rigorous assessment of outcomes over the entire course of a migraine attack, particularly between two and eight hours. Patients and experts described that to be effective, migraine medications need to work quickly and then remain active or be able to be re-dosed. The selection of a two-hour outcome focuses on quick action but may miss the time of maximal benefit if it is delayed. Data presented at the meeting on rimegepant and ubrogepant suggested that benefits continue to increase after two hours and that as a result, cost effectiveness looking at two-hour benefits may underestimate the true cost-effectiveness of these agents. Assessing primary outcomes over longer time periods in placebo controlled and/or active comparator studies would help address this issue.

(2) Manufacturers and researchers should develop comparative trials of acute treatments for migraine that assess whether new medications have a lower risk for medication overuse headache and can reduce the frequency of migraine attacks over time.

The use of single dose trials for FDA approval does not lead to comparative data that relate to how these new medications will be used in clinical practice where dosing with each new migraine attack is to be expected. Patient and experts highlighted the risk of medication overuse headache with frequent, repeat dosing of existing medications. It is uncertain whether this will be seen with the new medications. In addition, the potential for these new medications to decrease the frequency of headaches over time was highlighted. ICER did not consider these potential benefits in its cost-effectiveness models because of the lack of data or uncertainty about the effect or its magnitude.

(3) Manufacturers and researchers should conduct real-world comparative studies of acute treatments for migraine that assess important outcomes including quality of life, work, productivity and disability.

Patients highlighted the impact that frequent, severe migraine attacks over time can have on all aspects of life. As an episodic and chronic condition that affects patients throughout their lives, it can disrupt personal relationships with friends and family, and their ability to function at home and work. If the migraine attack is not aborted quickly and without medication related side effects, ability to work or work productively is profoundly affected. The combination of frequent, severe and unpredictable migraine attacks impacts ability to work, increases the risk of disability, and can

have a long-term negative economic impact on the patient and her/his family. Studies are needed to assess whether new treatments are effective in improving these important outcomes.

Regulators

(1) The patient population which may be considered for treatment with lasmiditan, rimegepant and ubrogepant is very large. Regulators have an important role to play in how new therapeutics enter clinical practice and therefore should require post-approval, long-term comparative outcomes studies for new acute treatments for migraine that are initially evaluated and approved in single-dose randomized trials.

The patient population which may be considered for acute treatment of migraine with these new medications is very large. Though triptans are effective and safe for many, patient advocates and experts highlighted that patients commonly end up looking for other treatments because of lack of effect, loss of efficacy, side effects or contraindications to their use. With lasmiditan and ubrogepant having received FDA approval and rimegepant likely to be approved shortly, clinical experts during the roundtable discussion highlighted the challenge of selecting which drug to use in which patient. Given the broad indications for these new medications, comparisons of the new drugs to each other, and to triptans among those who are triptan naïve are needed.

Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the January 23, 2020 Public meeting of the Midwest CEPAC.

Appendix Table 1. ICER Staff and Consultants and COI Disclosures

Name	Organization	Disclosures
Foluso Agboola, MBBS, MPH	Institute for Clinical and Economic Review	*
Steven Atlas, MD, MPH-DF/HCC	Harvard Medical School, Massachusetts General Hospital	*
Todd A. Lee, PharmD, PhD	University of Illinois at Chicago	*
Zunelly Odhiambo, MPH	Institute for Clinical and Economic Review	*
Steven D. Pearson, MD, MSc	Institute for Clinical and Economic Review	*
Michelle Poulin, BA	Institute for Clinical and Economic Review	*
David M. Rind, MD, MSc	Institute for Clinical and Economic Review	*
Matt Seidner, BS	Institute for Clinical and Economic Review	*
Daniel Touchette, PharmD, MA, FCCP	Institute for Clinical and Economic Review	*

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Appendix Table 2. Midwest CEPAC Panel Member Participants and COI Disclosures

Name	Organization	Disclosures
Eric Armbrecht, PhD	Associate Professor, Saint Louis University Center for Health Outcomes Research, School of Medicine, and College for Public Health & Social Justice	*
Nicholas Bagley, JD	Professor of Law, University of Michigan Law School	*
Bijan Borah, PhD	Professor of Health Services Research, Mayo Clinic College of Medicine and Science	*
Aaron Carroll, MD, MS	Professor of Pediatrics; Associate Dean for Research Mentoring; Director, Center for Health Policy and Professionalism Research, Indiana University School of Medicine	*
Don Casey, MD, MPH, MBA	Principal, IPO4Health; Senior Vice President and Chief of Clinical Affairs, Medecision	*
Gregory Curfman, MD	Deputy Editor, Journal of the American Medical Association (JAMA)	*
Stacie B. Dusetzina, PhD	Associate Professor of Health Policy, Ingram Associate Professor of Cancer Research, Vanderbilt University School of Medicine	*
Jill Johnson, PharmD	Professor, College of Pharmacy, University of Arkansas for Medical Sciences	*
Reem Mustafa, MD, MPH, PhD	Associate Professor of Medicine, Division of Nephrology and Hypertension, and Director, Outcomes and Implementation Research, University of Kansas Medical Center	*
Rachel Sachs, JD, MPH	Associate Professor of Law, Washington University in St. Louis	*
Kurt Vanden Bosch, PharmD	System Formulary Manager, St. Luke's Health System, Idaho	*
Stuart Winston, DO	Physician Lead: Patient Experience, Quality Improvement, Integrated Health Associates, St. Joseph Mercy Health System	*

*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Appendix Table 3. Policy Roundtable Participants and COI Disclosures

Name	Title and Affiliation
Harold Carter, PharmD	Senior Director, Clinical Solutions, Express Scripts
Erin G. Doty, MD	Senior Medical Advisor, Migraine and Headache Disorders, Eli Lilly
Katie Golden, BA	Director of Patient Relations, Immediate Past Steering Committee Member, Coalition for Headache and Migraine Patients
Christopher Gottschalk, MD, FAHS	Director, Headache Medicine; Chief, General Neurology; Yale School of Medicine
Gil L'Italien, PhD	Senior Vice President of GHEOR and Epidemiology, Biohaven Pharmaceuticals
Mitchell Mathis, MD	Vice President, Chief Medical Officer, CNS, Allergan
Travis Tacheny, PharmD	Clinical Pharmacy Program Consultant, HealthPartners
Sarah Wells Kocsis, MBA	Vice President of Public Policy, Society for Women's Health Research