Summary

WHAT IS MIGRAINE?

Migraine is a common cause of headache and is characterized by episodic, recurrent attacks that are classically pulsatile or throbbing, frequently involve one side of the head, and are associated with nausea and sensitivity to external stimuli such as light, sound, and smells. Migraine attacks vary in their frequency and intensity, but when severe can be a disabling, chronic condition that can impact all aspects of life including personal relationships and ability to work. An estimated 40 million adults or 12-15% of adults in the United States (US) report migraine or severe headaches.

TREATMENT OPTIONS

Standard management of migraine focuses on two strategies: preventive therapy to reduce the number of migraine attacks and acute therapy to relieve migraine symptoms after an attack begins. This review examines acute treatments for migraine. For individuals with mild symptoms, migraine can be treated with over the counter pain medications (e.g., ibuprofen, acetaminophen). For those with moderate or severe symptoms, the use of specific migraine medications is recommended. The most commonly used migraine specific medication class for acute treatment are "triptans". Though effective and safe for many patients with migraine, triptans may not be sufficiently helpful, can have intolerable side effects, or may have contraindications (e.g., patients with cardiovascular disease). For these reasons, new treatment options are needed.

Calcitonin gene-related peptide (CGRP) antagonists are an emerging class of drugs for acute treatment of migraine. On December 23, 2019, the first CGRP antagonist for the treatment of acute migraine, ubrogepant (**Ubrelvy**™, Allergan) was approved by the US Food and Drug Administration (FDA). Another CGRP antagonist, rimegepant, is currently under review by the FDA.

Lasmiditan (**Reyvow**™, Lilly), a selective 5-HT 1f agonist (triptans are 5-HT 1b/1d agonists), is another new acute treatment for migraine. It was approved on October 11, 2019 by the FDA.

KEY REPORT FINDINGS

- For those people with migraine who are not able to take triptans, results from clinical trials show that lasmiditan, rimegepant, and ubrogepant all decrease symptoms of migraine attacks and improve function compared with placebo. The evidence provides moderate certainty that all three treatments offer a small or substantial net health benefit, with high certainty of at least a small net health benefit.
- The evidence also suggests that rimegepant and ubrogepant provide comparable net health benefits to each other. Lasmiditan probably has similar efficacy to the other two medications but it also has significantly higher rates of dizziness and discontinuation.
- For patients with migraine who can take triptans, indirect comparisons suggest that triptans are similar or more effective than lasmiditan, rimegepant and ubrogepant.

POLICY RECOMMENDATIONS

- 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.
- 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.
- 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. Manufacturers should also conduct real-world comparative studies of acute treatments for migraine.

Clinical Analyses

How strong is the evidence that lasmiditan, rimegepant, and ubrogepant improve outcomes in patients with acute migraine?

ICER EVIDENCE RATINGS

Evidence ratings weighed uncertainties about potential harms of the treatments against the benefits. For all adults with acute migraine, the evidence provides high certainty of a comparable net health benefit between rimegepant and ubrogepant. For lasmiditan, there was moderate certainty that it offers a comparable or inferior net health benefit compared to rimegepant and ubrogepant.

	Lasmiditan	Rimegepant	Ubrogepant
For adults with moderate-severe migraine attacks that have not responded to non-prescription medicines and for whom triptans have not been effective, are not tolerated, or are contraindicated	Moderate certainty of a small or substantial health benefit compared to no treatment	Moderate certainty of a small or substantial health benefit compared to no treatment	Moderate certainty of a small or substantial health benefit compared to no treatment
For adults with acute migraine who can tolerate triptans	Comparable or inferior net health benefit to triptans	Comparable or inferior net health benefit to triptans	Comparable or inferior net health benefit to triptans

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

How effective are these therapies?

Results from placebo controlled clinical trials suggest that lasmiditan, rimegepant and ubrogepant decrease symptoms of migraine attacks (pain, phonophobia, photophobia, or nausea) and improve function compared to placebo at two hours.

	Patients with “no pain” at 2 hours (pain freedom)	Patients free of most bothersome symptom (phonophobia, photophobia, or nausea) at 2 hours	Patients achieving full function at 2 hours
Lasmiditan vs. placebo	↑	↑	↑
Rimegepant vs. placebo	↑	↑	↑
Ubrogepant vs. placebo	↑	↑	↑

Clinical Analyses (continued)

Additional analyses conducted by ICER suggest no difference between lasmiditan, rimegepant and ubrogepant in decreasing symptoms of migraine attacks (pain, phonophobia, photophobia, or nausea) and improving function at two hours. However, compared to triptans (sumatriptan and eletriptan), ICER's analyses suggest that lasmiditan and CGRP antagonists were less effective in decreasing symptoms of migraine attacks at two hours.

HARMS

Overall, the adverse events (AEs) observed in clinical trials were mild or moderate in intensity. Nausea was the most commonly reported AE in the rimegepant and ubrogepant trials.

In the lasmiditan trials, central nervous system-related AEs like dizziness, excess sleepiness, and a tingling sensation were the most frequently reported. Higher rates of discontinuation was observed in the long-term trials of lasmiditan compared to rimegepant and ubrogepant. Due to concerns about excessive sleepiness with lasmiditan, the FDA label advises that patients should not drive or operate machinery within eight hours of taking a lasmiditan dose.

SOURCES OF UNCERTAINTY

Lack of head-to-head studies: We used indirect analyses to compare lasmiditan, rimegepant and ubrogepant to each other, and to triptans due to lack of head-to-head studies.

Patient important outcomes: The primary outcomes reported included efficacy and side effects of a single dose of each drug compared to placebo at two hours after initial study medication. Though patients highlighted the importance of outcomes after two hours, protocols for use of rescue medications differed among trials, which made it difficult to assess the benefits of these drugs after two hours.

Durability of effect: Most data for these drugs came from trials treating a single migraine attack; outcomes when used over time for repeated attacks are uncertain.

Minimal long-term safety data for new therapies: Triptans are considered to have safety concerns related to vasoconstrictive effects and, when used with certain other medications such as SSRIs, carry a risk of serotonin syndrome, although decades of use have suggested that these complications may be extremely infrequent in clinical practice. In contrast, the newer agents which appear to be potentially safer have much less clinical information to demonstrate long-term safety at this time.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS

Do these treatments meet established thresholds for long-term cost-effectiveness?

For adults with moderate-severe migraine attacks patients **for whom triptans are not effective, not tolerated, or are contraindicated**:

- Lasmiditan exceeds commonly accepted thresholds for cost-effectiveness of $50,000-$150,000 per quality-adjusted life year (QALY) at the estimated net price when compared to placebo
- Both ubrogepant and rimegepant* fall below commonly cited thresholds for cost-effectiveness at the estimated net price when compared to placebo

	Lasmiditan vs. placebo	Rimegepant* vs. placebo	Ubrogepant vs. placebo
Cost per QALY gained	$151,800	$39,800	$40,000

* The price for rimegepant was assumed to be the same as ubrogepant.

For adults with acute migraine **who can tolerate triptans**, sumatriptan and eletriptan are both more effective and less expensive than these newer agents.

Because none of these treatments has been shown to extend patients' lives, ICER did not calculate what prices would be needed to reach alternative cost-effectiveness thresholds based on equal value of Life Years Gained (evLYG).

Economic Analyses (continued)

VALUE-BASED PRICE BENCHMARKS

What is a fair price for these therapies based on its value to patients and the health care system?

	Lasmiditan	Rimegepant	Ubrogepant
Annual Price to Achieve $100,000 - $150,000/QALY Threshold	$2,900-$3,348	$4,160-$4,640	$4,150-$4,630

Lasmiditan's annual list price of $4,610 is higher than ICER's value-based price benchmark range of $2,900-$3,348. Rimegepant's assumed annual list price of $4,896 is higher than ICER's value-based price benchmark range of $4,160-$4,640. Finally, ubrogepant's annual list price of $4,896 is higher than ICER's value-based price benchmark range of $4,150-$4,630.

POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients can be treated before crossing ICER's $819 million budget impact threshold?

Lasmiditan: At its current list price, approximately 12% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million per year.

Rimegepant: At its current placeholder list price, approximately 16% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million per year.

Ubrogepant: At its current list price, approximately 16% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $819 million per year.

Voting Results

The Midwest CEPAC deliberated on key questions raised by ICER's report at a public meeting on January 23, 2020. The results of the votes are presented below. More detail on the voting results is provided in the full report.

CLINICAL EVIDENCE

- All panelists found adequate evidence to demonstrate a net health benefit for treatment with lasmiditan, rimegepant, or ubrogepant compared with no treatment.
- All panelists found that the evidence was insufficient to distinguish the net health benefit between rimegepant and ubrogepant.
- A majority of panelists found the evidence insufficient to distinguish the net health benefit among lasmiditan, rimegepant, or ubrogepant.
- All panelists found the evidence to be insufficient to demonstrate superior net health benefit for lasmiditan, rimegepant, or ubrogepant compared to triptans.

LONG-TERM VALUE FOR MONEY

- A majority of panelists found ubrogepant represented an intermediate long-term value for money compared to no treatment. However, this vote was taken before additional analyses were incorporated into the base case and reflected uncertainty as to which analysis to focus on.

OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

- A majority of panelists found the "gepants" and lasmiditan offered a novel mechanism of action or approach that will allow successful treatment of many patients for whom other treatments have failed.
- A majority of panelists found that treating patients with "gepants" will offer reduced complexity that will significantly improve patient outcomes compared to treatment with lasmiditan.
- A majority of panelists found the "gepants" and lasmiditan are intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.

Policy Recommendations

For Payers

- 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 CGRP drug should a trial of the favored drug not produce adequate success.

For Providers

- 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.

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

For Manufacturers and Clinical Societies

- 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.

- 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.

For Regulators

- 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.

About ICER

TThe Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer-review.org).