

Overview: About Migraine

WHAT IS MIGRAINE?

Migraine is a common, recurrent headache disorder that affects approximately 20% of women and 6-10% of men in the US. Migraine attacks are characterized by moderate-to-severe pain and other symptoms, which may persist between attacks. Those with severe symptoms may require bed rest and experience disability that affects school, employment, choice of leisure activities, interpersonal relationships, and more.

Migraine can be classified as **chronic**, defined as 15 or more headache days per month for at least three months, or as **episodic**, which is fewer than 15 days. In the US, approximately 10% of those with migraine have the chronic form.

HOW IS MIGRAINE TREATED?

For many, migraine can be treated with oral pain relievers, but those with severe disease typically try multiple therapies, including both non-drug (e.g., exercise, diet, relaxation techniques) and drug therapies. **Acute drug therapies**, such as triptans, treat symptoms after they've started. **Preventive drug therapies** decrease the frequency and/or severity of attacks and include certain antidepressants, anti-seizure medications, beta-blockers, and, for those with chronic migraine, onabotulinum toxin A (Botox®, Allergan plc). For many people, preventive therapies are not effective or have intolerable side effects.

Calcitonin gene-related peptide (CGRP) inhibitors are an emerging class of drugs for migraine prevention. In May 2018, erenumab (Aimovig™ Amgen, Inc. and Novartis AG) was approved in the US as a preventive therapy for use in both episodic and chronic migraine. Two additional CGRP inhibitors, fremanezumab (Teva Pharmaceuticals) and galcanezumab (Eli Lilly and Company) are under FDA review at the time of this report.

Summary

ICER's report was reviewed at a public meeting of the California Technology Assessment Forum (CTAF) on June 14, 2018. A majority of the independent voting panel found that, when balancing the benefits and potential risks of therapy, evidence shows a net health benefit for patients with chronic migraine and no other treatment, but is currently inadequate to show a benefit in those with less frequent migraine.

POLICY IMPLICATIONS

Key policy implications from the review include:

- Given the new mechanism of action, limited long-term safety and efficacy data, and FDA label that could suggest broad eligibility, it is reasonable for payers to develop prior authorization criteria to ensure prudent use of CGRP inhibitors.
- Following the example set by the first CGRP inhibitor, manufacturers should continue to exercise restraint in pricing and price negotiation so that net prices align with added benefits. Future consideration of increases should be justified by new clinical evidence of superior performance.
- Clinicians should be aware of the uncertainties in long-term efficacy and potential harms when prescribing CGRP inhibitors.

Clinical Analyses: ICER Evidence Ratings

How strong is the evidence that CGRP inhibitors improve outcomes in patients with migraine?

Evidence ratings weighed uncertainties about potential harms of CGRP inhibitors against the need for therapy in patients without other preventive treatment options. Evidence was insufficient to differentiate the net health benefit of erenumab, fremanezumab, and galcanezumab for all populations and comparisons.

Chronic Migraine			
	Erenumab	Fremanezumab	Galcanezumab
Patients eligible to receive preventive therapy with oral agents or onabotulinum toxin A	Insufficient	Insufficient	Insufficient based on limited number of published studies
Patients for whom prior preventive therapy has failed	Comparable or better	Comparable or better	Insufficient based on limited number of published studies
Episodic Migraine			
	Erenumab	Fremanezumab	Galcanezumab
Patients eligible to receive preventive therapy with oral agents	Insufficient	Insufficient	Insufficient
Patients for whom prior preventive therapies have failed	Promising but Inconclusive	Promising but Inconclusive	Insufficient based on limited number of published studies

Clinical Analyses (continued)

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Results from clinical trials and ICER’s analyses suggest that preventive treatment with CGRP inhibitors provide **some clinical benefit** in patients with chronic or episodic migraine compared with no treatment. Average reductions in migraine days account for placebo effect.

Chronic Migraine			
	Monthly Migraine Days	Days Using Acute Medications	
Erenumab	 About 2 fewer days	 About 2 fewer days	
Fremanezumab	 About 2 fewer days	 About 2 fewer days	
Episodic Migraine			
	Monthly Migraine Days	Days Using Acute Medications	50% Responders*
Erenumab	 About 2 fewer days	 About 2 fewer days	
Fremanezumab	 About 2 fewer days	 About 1 less day	
Galcanezumab	 About 2 fewer days	 About 2 fewer days	

*Patients experiencing at least a 50% decrease in monthly migraine days

ICER also reviewed monthly migraine day data for the subpopulation of chronic migraine patients for whom at least one prior preventive therapy had failed; manufacturers of erenumab and fremanezumab submitted the data in confidence. As per ICER’s data in confidence policy, these results are redacted in the full report, but will be unmasked no later than December 2019.

Clinical Analyses (continued)

HARMS

Overall, the CGRP inhibitors were well-tolerated in trials; however, little is known about their long-term effects. The harms that were seen in trials were generally nonserious and uncommon. The most common were:

- Injection-site reactions in up to 30% of patients
- Cold symptoms and upper respiratory tract infection in less than 12% of patients

In the trials of other preventive therapies, the most commonly reported adverse events were fatigue, difficulty with memory, concentration, or language, prickling sensation, changes in taste, and weight change. These events were not frequently observed in the CGRP inhibitor trials.

SOURCES OF UNCERTAINTY

Trial Duration: Trials assessed outcomes by 12 or 24 weeks, and uncertainty remains around the durability of effects or adverse events from long-term use.

Rare Harms: These interventions are the first in the CGRP inhibitor class, and rare adverse events could have been missed in the clinical trials.

Length of treatment: There is little evidence on optimal duration of preventive treatments, both for the existing preventives and the CGRP inhibitors.

Patient Outcomes: Outcomes studied in trials do not address many of the outcomes important to patients. Patients expressed a desire to see the effects of these therapies on daily activities; however, quality of life measures were infrequently reported; when reported, modest improvements were seen compared to other therapies.

Generalizability: Trials did not study the safety and efficacy of CGRP inhibitors in migraine patients who are pregnant or have other comorbidities, and data on patients for whom multiple preventive therapies have failed are limited.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS

Do CGRP inhibitors meet established thresholds for long-term cost-effectiveness?

ICER’s economic analyses found that, at a net price of \$5,000*, the use of CGRP inhibitors in patients for whom prior preventive therapy failed **meets commonly accepted thresholds for cost-effectiveness** of \$100,000-\$150,000 per quality-adjusted life year (QALY) gained when compared to placebo.

Chronic Migraine		Episodic Migraine	
Treatment	Cost per QALY Gained	Treatment	Cost per QALY Gained
Erenumab	\$90,000	Erenumab	\$150,000
Fremanezumab	\$120,000	Fremanezumab	\$150,000

*Net price calculated using erenumab’s announced list price of \$6,900 annually, net of an estimated 27% discount, the industry-wide average for branded drugs. As fremanezumab is still under FDA review, a price is not available, and erenumab’s price was used as its estimated price.

VALUE-BASED PRICE BENCHMARKS

What is a fair price for CGRP inhibitors based on their value to patients and the health care system?

The \$5,000 assumed net price of CGRP inhibitors **aligns with the benefits** they provide to patients with chronic and episodic migraine for whom prior preventive treatments have failed.

	Annual WAC*	Annual Net Price**	Annual Price to Achieve \$100,000–\$150,000 per QALY	Discount from WAC to Reach Threshold Prices
Erenumab	\$6,900	\$5,000	\$3,700–\$5,300	23% to 46%
Fremanezumab	\$6,900	\$5,000	\$3,700–\$5,200	25% to 46%

*Wholesale acquisition cost

**Net price calculated using erenumab’s announced list price of \$6,900 annually, net of an estimated 27% discount, the industry-wide average for branded drugs. As fremanezumab is still under FDA review, a price is not available, and erenumab’s price was used as its estimated price.

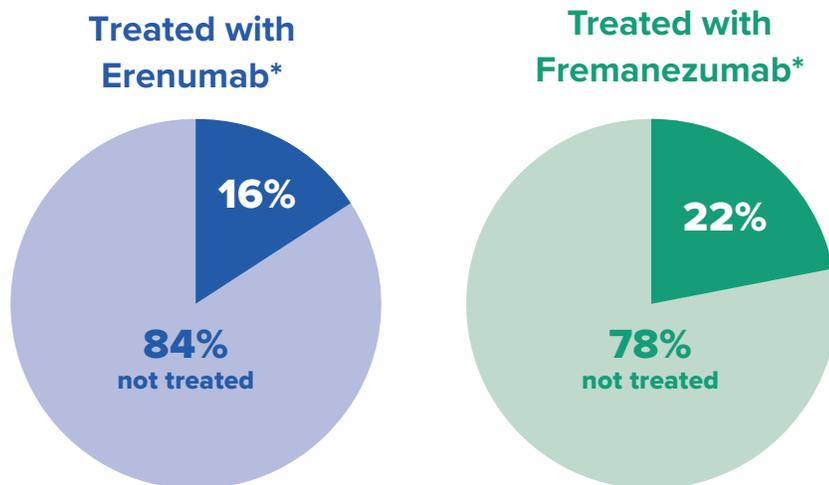
Economic Analyses (continued)

POTENTIAL SHORT-TERM BUDGET IMPACT

How many patients can be treated with CGRP inhibitors before crossing ICER’s \$915 million budget impact threshold?

ICER’s analyses estimated that approximately 4.5 million people with episodic migraine and 1.1 million people with chronic migraine, all for whom at least one prior preventive therapy has failed, would be eligible for treatment with a CGRP inhibitor.

At an assumed net price of \$5,000, ICER estimates that 16% of eligible patients could be treated with erenumab and 22% could be treated with fremanezumab, annually, without raising concerns about affordability. It is unknown at this time how many individuals within the eligible population will be prescribed a CGRP inhibitor.



**Using net price of erenumab.*

ACCESS AND AFFORDABILITY

As illustrated in these analyses, treating the entire patient population eligible for treatment with CGRP inhibitors would have a substantial budget impact. However, at the June 14 public meeting, clinical experts indicated that uptake is unlikely to exceed levels that would threaten access and affordability, as CGRP inhibitors use a novel mechanism of action with an unknown long-term safety profile, are injectable, and patients who do not benefit from therapy are likely to discontinue treatment. As such, ICER is not issuing an access and affordability alert at this time. However, given the budget impact potential, all stakeholders should closely monitor the use of CGRP inhibitors in the event that actual uptake exceeds expectations.

Voting Results

CTAF deliberated on key questions raised by ICER's report at a public meeting on June 14, 2018. More detail on the voting results is provided in the [full report](#).

CLINICAL EFFECTIVENESS

- Evidence was adequate to show a net health benefit of the CGRP inhibitors for individuals with chronic migraine and no other available treatment options.
- While acknowledging the significant impact episodic migraine has on day-to-day life, Panel members pointed to the unknown long-term risks and voted that current evidence is inadequate to show a net health benefit of the CGRP inhibitors for individuals with episodic migraine.
- Evidence was voted insufficient for CGRP inhibitors compared to oral agents or onabotulinum toxin A (Botox®, Allergan) in those with chronic migraine, and compared to oral agents in episodic migraine.

OTHER BENEFITS AND CONTEXTUAL CONSIDERATIONS

- Panel members noted that the therapies may provide potential additional benefits beyond those studied in clinical trials, including reduced family/caregiver burden, a novel mechanism of action, and increased productivity. Further, the high severity and lifetime burden of illness, along with the significant uncertainty around long-term risks and the magnitude and durability of benefit, were noted as key contextual considerations that factored into CTAF's assessment of value.

LONG-TERM VALUE FOR MONEY

- A majority of the panel voted that erenumab represents an intermediate value in adults with chronic migraine, and votes were split between intermediate and low for those with episodic migraine.

Key Policy Implications

The CTAF Panel participated in a moderated policy discussion that included physicians, patient advocates, manufacturer representatives, and payer representatives. None of the resulting policy statements should be taken as a consensus view held by all participants. For a more detailed discussion, please see the [full report](#).

PAYERS

- Given that CGRP inhibitors have a new mechanism of action, are entering clinical use without long-term safety and efficacy data, and were labeled by the FDA using language that could suggest that all patients with migraine are eligible for treatment, it is reasonable for insurers and other payers to develop prior authorization criteria to ensure prudent use of these treatments.
- When responsible pricing is accomplished and the net price of CGRP inhibitors aligns with the estimated added benefit for patients, prior authorization criteria should be relatively streamlined and allow documentation of eligibility through a clinician statement that patients have attempted adequate trials of two to three other preventive therapies rather than requiring extensive submission of clinical documents.
- Payers should negotiate discounts to seek the best value for patients and the health system by bringing the net price into traditional cost-effectiveness ranges. Adequate discounts may require preferential formulary placement for one particular CGRP inhibitor, but payers should maintain options for clinicians and patients to seek coverage for more than one CGRP inhibitor.
- Prior authorization criteria should be based on clinical evidence with input from clinical experts and patient groups. Options for specific elements of coverage criteria within insurance coverage policy include:
 - ▶ Potential patient eligibility criteria: Adults with migraine with four or more headache days per month, and patients with inadequate response to treatment with two/three other migraine preventive medications and a reasonable trial of one or more triptan medications.
 - ▶ Potential provider criteria: CGRP inhibitors can be covered if prescribed by any clinician – or – CGRP inhibitors may be covered only if prescribed by a specialist clinician with formal training in neurology or pain management.
 - ▶ Potential limitations on initial length of coverage: Ongoing coverage may require that clinicians attest to clinical improvement after some pre-specified length of treatment (e.g. 3–6 months) – or – no limitation on length of coverage may be required for CGRP inhibitors.

Key Policy Implications (continued)

MANUFACTURERS

- Following the example set by the launch of the first CGRP inhibitor, manufacturers should continue to exercise restraint in pricing and price negotiation with payers so that net prices align reasonably with the added benefits for patients. Consideration of price increases in future years should be transparently justified by new clinical evidence of superior performance.
- Manufacturers should exercise restraint in marketing CGRP inhibitors to incorporate the reality that patients will be required to have tried other preventive options first. Promotional material for patients and for clinicians should explicitly refrain from building unrealistic expectations of a cure.
- Manufacturers and researchers should support studies that evaluate the efficacy of CGRP inhibitors in the patients most likely to receive them: those for whom multiple prior preventive therapies have failed.

- Manufacturers and researchers should conduct studies directly comparing CGRP inhibitors and other treatment options using standardized research protocols and outcome assessments to permit real-world, long-term outcome assessment.

PATIENTS

- Patient groups should advocate early during trial development to ensure evidence on the outcomes most important to patients is available at the time of product launch.

PROVIDERS

- Clinicians should be aware of the uncertainties in long-term efficacy and potential harms when prescribing CGRP inhibitors.

About ICER

The 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).