Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value

Final Background and Scope

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Background

Migraine is a common, recurrent headache disorder that affects approximately 18% of women and 6% of men in the United States (US).[1] Migraine can be subclassified into chronic migraine, which is characterized by 15 or more headache days per month for at least three months, of which migraine features are present on at least eight days per month.[2] Migraine not subclassified as chronic migraine has been called "episodic migraine," although this term is not a clinical diagnosis. We use the term "episodic" in this document to refer to such patients. In the US, approximately 90% of patients with migraine have episodic migraine and 10% have chronic migraine.[1,3]

Migraine is among the top ten causes of years lived with disability in the US.[4,5] When a patient experiences a migraine, she or he may feel moderate-to-severe pain and other symptoms (e.g., nausea, vomiting, or sensitivity to light or to sound), have a reduced ability to function, or require bed rest.[1] Between migraine attacks, pain and other symptoms may remain, and patients' neurological function may not return to normal (pre-headache).[6] Hence, the duration of impairment may be longer than the migraine attack itself, which can lead to ongoing disability.[7-9] Migraine also may affect school, employment, choice of leisure activities and foods, and interpersonal relationships.[10-12] In addition, patients with migraine are stigmatized through their experiences being devaluated or discriminated against, which disrupts quality of life and ability to work.[13]

Despite its high prevalence and impairment, migraine is often not recognized or effectively treated.[3,14] Patients typically try multiple therapies, including non-pharmacologic therapies (e.g., exercise, changes in diet, relaxation techniques, cognitive behavioral therapy[7]) and pharmacological therapies. Migraine therapies can be broadly categorized into those used for treatment once symptoms have started ("acute" or "abortive" treatments) and those used to decrease the frequency or severity of migraines ("preventive" or "prophylactic" treatments). Although there are no strict guidelines on who should receive preventive therapy, those who have four or more migraines per month or who have headaches lasting more than 12 hours are typically considered candidates for preventive therapy. Effective preventive pharmacological therapies include some

antidepressants (amitriptyline, venlafaxine), anti-seizure medications (divalproex sodium, sodium valproate, topiramate), and beta-blockers (e.g., propranolol, metoprolol).[15] Patients with chronic migraine may also use onabotulinum toxin A (Botox®, Allergan plc) injections for prevention. Patients on preventive therapy frequently discontinue or switch treatments due to lack of efficacy or tolerability.[7] Adequate therapeutic trials of preventive therapies may require two to six months of treatment.[16] Without adequate treatment, patients with episodic migraine are more likely to progress to chronic migraine.[17]

The calcitonin gene-related peptide (CGRP) pathway is important in pain modulation, and new agents affecting that pathway are being developed and studied. Erenumab (Amgen, Inc. and Novartis AG), a fully human monoclonal antibody that binds to the CGRP receptor, has been assessed as a preventive therapy in both episodic and chronic migraine patients.[18-20] Fremanezumab (Teva Pharmaceuticals) and galcanezumab (Eli Lilly and Company), two humanized monoclonal antibodies that target the CGRP ligand, have also been studied in migraine patients.[21-24] The FDA is currently evaluating erenumab with a decision expected in May 2018;[25] fremanezumab in the first half of 2018;[26] and galcanezumab in the third quarter of 2018.[27] The potential use of CGRP inhibitors has generated great interest from clinicians, patients, and their families. Nevertheless, uncertainties remain regarding the effectiveness of CGRP inhibitors compared with existing preventive therapies and with each other, and how well the potential cost of CGRP inhibitors will align with potential patient benefits. Therefore, stakeholders will benefit from a comprehensive review of the clinical evidence and potential economic impact.

Stakeholder Input

This scoping document was developed with input from a diverse group of stakeholders, including patients and their families, clinicians, researchers, representatives from pain and migraine foundations, and manufacturers of the agents of focus in this review. The draft scoping document incorporated feedback gathered during preliminary calls with stakeholders and open input submissions from the public. Based on feedback on the draft scope, the document has been revised to clarify the patient populations and comparators of interest for both the systematic review and the economic model.

From the open input period, we heard extensively from migraine patients about how living with migraine affects their everyday lives, how current treatments provide only temporary relief, how accessing effective care or treatment is challenging, and what outcomes are most important. Below, we provide a summary of the main themes from these submissions.

Migraines prevent patients from having normal lives:

- The pain and other symptoms from migraines can last from hours to days.

- Migraines alter patients' decisions, and many patients do not plan or commit to future events because of the uncertainty surrounding when the next attack will occur.
- Patients frequently reported feeling frustrated, depressed, defeated, isolated, or a burden to society; some patients have expressed suicidal thoughts.
- Patients can miss many days of work or school per month due to migraine attacks.
- At work or school, patients struggle to concentrate, remember things, or speak clearly, which affects performance and employment.
- Relationships with family and friends are strained because of unpredictability of migraine attacks, difficulties participating in activities, and financial pressures from migraine-related medical expenses.
- Patients feel stigmatized and that migraine pain is not taken seriously.

Relief from existing preventive treatments is often temporary:

- Patients have tried extensive lists of preventive and abortive treatments (including drug and non-drug therapies, lifestyle changes).
- Some treatments work for a time, but they either stop working or are not tolerable.
- Side-effects from some interventions can be as debilitating as the migraines.

Patients struggle to access effective care or treatment:

- Difficulties arise in finding a physician who understands migraine and migraine pain.
- Due to high costs and access restrictions, patients may not have a sufficient supply of treatment; patients may ration treatment and choose the “important” days to take treatment.
- Patients feel discouraged because treatment strategies follow a “guess and test” procedure, which can take many years before they find an effective treatment.
- Patient reported paying high co-pays for many treatments; some patients must wait for pre-authorization from their insurer; patients also are concerned about the ability to afford new treatments.

Patients seek treatments that improve their quality of life

- For many patients, reduced pain and symptom relief are important steps to improving overall quality of life.
- Patients also reported that fewer side-effects, improved cognitive functioning, and ability to work or take care of family are important outcomes.

While many of the above comments have been incorporated into this scoping document, the Evidence Report will provide additional details of these patient-centric considerations. ICER looks forward to continued engagement with stakeholders throughout its review and encourages

comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Report Aim

This project will evaluate the health and economic outcomes of CGRP inhibitors as a preventive treatment for patients with episodic or chronic migraine. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms - including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs - are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

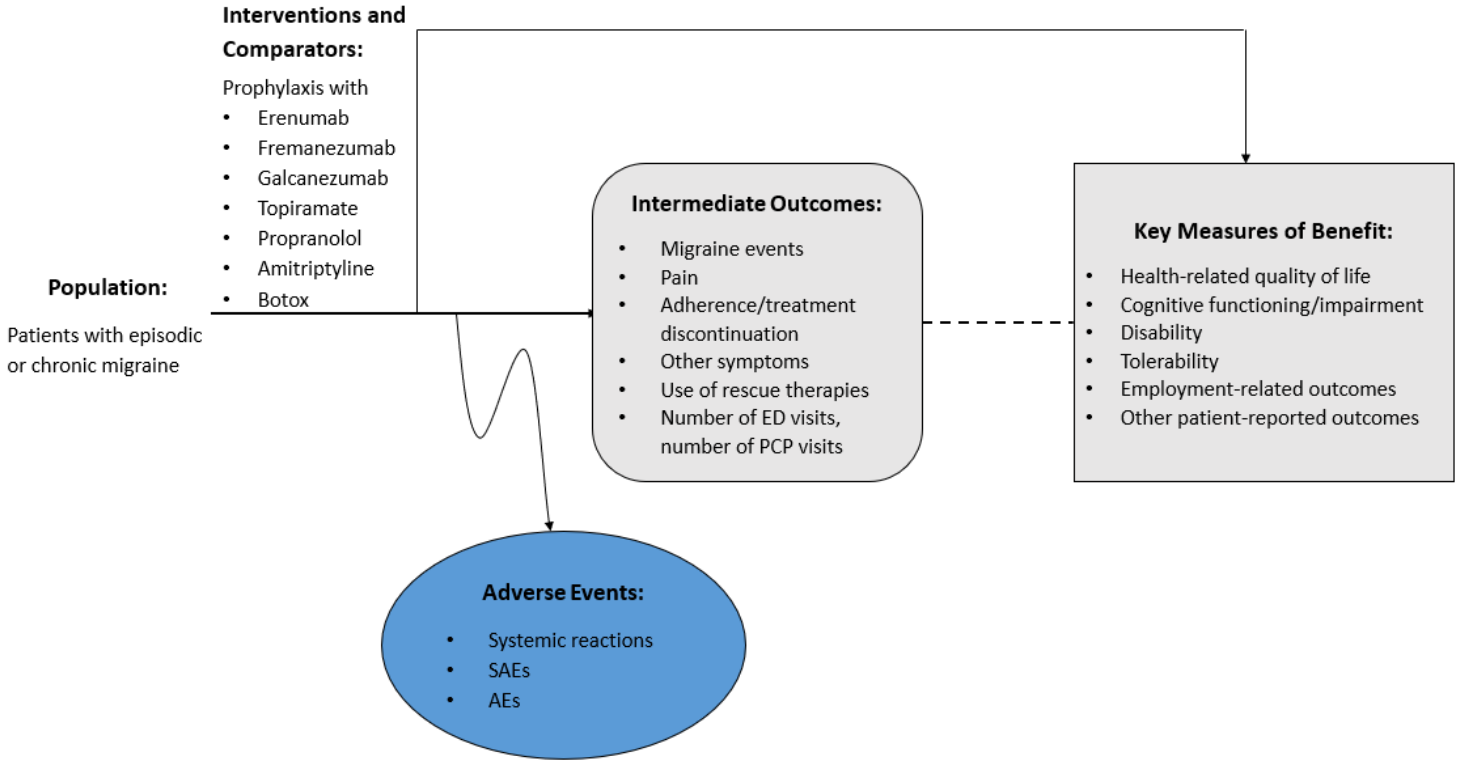
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the finalized scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Analytic Framework

The general analytic framework in Figure 1.1 on the following page illustrates the scope of this review.

Figure 1.1. Analytic Framework: CGRP Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine



AE: adverse event, ED: Emergency Department, PCP: Primary Care Physician, SAE: serious adverse event

The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes: those within the rounded boxes are intermediate outcomes (e.g., migraine events), and those within the squared-off boxes are key measures of benefit (e.g., health-related quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipsis.[28]

Populations

The population of focus for this review will be adult patients 18 years or older experiencing ≥ four headache days per month eligible for preventive therapy. We will evaluate the following two subpopulations:

1. Patients experiencing episodic migraine
2. Patients experiencing chronic migraine

As discussed above, adequate therapeutic trials of preventive therapies generally require two to six months of treatment. We heard from clinicians and patients that requiring failure of multiple classes of medications for prevention of episodic migraine prior to treatment with a CGRP inhibitor would typically take more than 18 months and may be overly burdensome. As such, we plan to assess CGRP inhibitors in patients who have not necessarily failed all or nearly all other classes of preventive therapies. Data permitting, we will evaluate subgroups defined by prior failure of other preventive treatments (e.g., 0, ≥ 1, ≥ 2 prior failures).

Interventions

The interventions of interest will be prophylactic treatment by subcutaneous injection of erenumab, fremanezumab, and galcanezumab.

Comparators

For each population and subgroup, we will compare the CGRP inhibitors to each other, to commonly-used migraine preventive therapies, and to no preventive therapy as data permit. For the episodic migraine population, the commonly-used preventives include topiramate, propranolol, and amitriptyline. For the chronic migraine population, the commonly-used preventives include topiramate, propranolol, amitriptyline, and onabotulinum toxin A. The CGRPs may be used alone or in combination with existing preventives (i.e., as add-on), and we will evaluate these cases separately as data permit.

Outcomes

The outcomes of interests include:

- Frequency, intensity, and duration of migraine events
- Pain
- Other symptoms: nausea, vomiting, dizziness, and sensitivity to light, sound, smell, or touch
- Cognitive functioning/impairment
- Disability
- Health-related quality of life

- Other patient-reported outcomes (e.g., depression, anxiety, and difficulties in interpersonal relationships)
- Employment-related outcomes (e.g., unemployment, work productivity loss, absenteeism)
- Use of rescue therapies
- Number of ED and primary care visits
- Adherence/treatment discontinuation
- Tolerability
- Harms/adverse events

All endpoints related to each of the above outcomes are of interest for this review. For example, the outcome "frequency of migraine events" encompasses endpoints for the percentage of patients with at least 50% fewer migraines per month and the mean change in the number of migraine days per month, among others.

Timing

Evidence on intervention effectiveness and harms will be derived from studies of any follow-up duration.

Settings

All relevant settings will be considered, including inpatient, outpatient/clinic, office, and home settings.

Other Benefits and Contextual Considerations

Our reviews seek to provide information on other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in the table on the following page.

Table 1.1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop two semi-Markov decision analytic models, one for episodic migraine and one for chronic migraine, to assess the lifetime cost-effectiveness of erenumab, fremanezumab, and galcanezumab relative to currently used preventive treatments in episodic and chronic migraine. For any intervention for which there is inadequate data, an economic evaluation will not be conducted. The model structure will be based in part on a literature review of prior published models of episodic and chronic migraine.[29-33] The base-case analysis will take a health-care system perspective (i.e., focus on direct medical care costs only). A modified societal perspective that includes productivity losses due to migraine will be considered in a separate analysis based on data available from the literature. In addition, if data allow, scenarios including potential effects on opioid use and associated costs and outcomes will be modeled.

For each of the CGRP inhibitors, and separately for episodic and chronic migraine, the "CGRP treatment" arm of the model will consist of the following discrete health states: 1) on treatment with migraine; 2) discontinuing treatment with migraine; and 3) death. A cohort of patients will transition between states using monthly cycles over a time horizon that is consistent with available evidence on adherence to prophylactic medications, modeling patients from treatment initiation until death. Based on data available in the literature, a comparison group, called the "no CGRP treatment group," will be modeled to represent patients not receiving any of the new agents but with outcomes and costs based on current treatment patterns for episodic and chronic migraine in the United States. In addition, cost-effectiveness will be estimated for several time horizons as data permit.

The key model inputs will include the number of monthly migraine days, quality of life, and health care costs. Migraine rates, total costs, and other outcomes will depend on the effectiveness of each intervention. Treatment effectiveness will be estimated using measures reported in the clinical trials, such as the reduction in the number of monthly migraine days associated with each treatment. Data permitting, findings from potential network meta-analyses or other systematic reviews will be used to compare interventions.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcomes of the new treatments will be evaluated relative to the "no CGRP treatment" group in terms of clinical outcomes such as migraine days avoided and quality-adjusted life years (QALYs) gained. Quality of life weights will be applied to each health state, including quality of life decrements for each migraine experienced and for serious adverse events. The model will include direct medical costs including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the incremental cost per QALY gained. We will also express results in terms of incremental cost per consequence; measures to be considered include cost per migraine day averted and cost per 50% reduction in migraine days. In addition to a robust set of sensitivity analyses (one-way, threshold, and probabilistic), the impact of changing key assumptions related to treatment patterns in the treated and untreated arms of the model will be evaluated. A detailed version of our methodologies for this economic evaluation will be available in our model analysis plan, which will be posted to the aforementioned Open Science Framework website.

In separate analyses, we will explore the potential health system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relationship between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by CGRP inhibitors (e.g., reduced use of rescue medication, fewer ED visits, etc.), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of episodic and chronic migraine beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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