May 2, 2018

Submitted electronically to: publiccomments@icer-review.org

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Boston, MA 02109

Re: Feedback on Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value, Draft Evidence Report Dated April 11, 2018

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide feedback on the Institute for Clinical and Economic Review's draft report on the effectiveness and value of CGRP inhibitors as preventive treatments for patients with episodic or chronic 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 more than 800 physician advocates committed to patient access. IfPA is a 501(c)(3) public charity non-profit organization.

Feedback on Draft Report

Migraine is one of the most prevalent neurological disorders worldwide, associated with substantial health, sociological and economic consequences.

Yet ICER's draft evidence report, dated April 11, 2018, inaccurately assesses the benefits that migraine patients can receive from CGRP inhibitors. This inaccuracy arises because: (1) the evidence that is necessary to evaluate the cost-effectiveness of CGRP inhibitors does not yet exist; (2) the draft evidence report inappropriately assumes that the CGRP inhibitors will have no impact on mortality rates; (3) the draft evidence report does not adequately consider the comorbidity of depression; and, (4) the draft evidence report does not consider the impact of

CGRP inhibitors on the vast and costly opioid crisis in the United States. A further concern is: (5) the draft evidence report fails to report fundamental data relied upon when performing the analysis.

1. Due to the timing of ICER's study, data limitations meaningfully restrict the draft evidence report's ability to evaluate the cost-effectiveness of CGRP inhibitors. Specifically, the CGRPs studied were either in phase II or III clinical trials, and none had yet secured FDA approval. Therefore, the clinical and safety data that is available for these medicines is limited; and importantly, the information on these medicines that will be gained from post-marketing studies is not yet available.

In particular, due to the novelty of these medicines, there is no available data on the long-term benefits of CGRP inhibitors. Nor is there information on patients' long-term adherence rates to these medicines. These data limitations raise other concerns, including:

- As noted in the draft evidence report, a short-term time frame (a two-year period) was used to evaluate the long-term impact of CGRP inhibitors "…because there is a lack of data on the long-term use of preventive medications for management of migraine" (p. 52-53). Extrapolating the long-term effects from short-term data introduces unknown biases into the analysis. In fact, in the limitations sections, ICER notes that "the models were based on *clinical trial results that may not hold true for longer time horizons* or in particular patient populations different than those seen in the trials" (p. 81, emphasis added). Simply noting this limitation does not eliminate the concerns, however.

- When creating the five-year annualized potential budget impact, the draft evidence report states "since people with migraine tend to cycle through several preventive therapies and since we have no long-term data on CGRP usage, we assumed that each sub-cohort (i.e., 20% of the prevalent cohort) remained in the model for two years, and a new cohort entered the model every year, resulting in larger patient populations for years two through five" (p. 86). No evidence justifies whether such assumptions are valid or not. Since usage is a fundamental input into the model, it should be based on actual long-term usage data, or reasonable proxies of this data, rather than arbitrary usage assumptions.

- CGRPs do not, as of yet, have publicly available prices. To overcome this problem, ICER uses an "analyst-estimated" price of $8,500 per year for all three drugs. There is no way to know whether these estimated prices reflect the actual market prices that will prevail for the CGRP medicines once they are available. If the estimated prices vary significantly from the actual market prices, then the validity of the cost-effectiveness calculations will be compromised. The draft evidence report notes these concerns as well, stating "the placeholder price estimate for the drugs may not reflect actual market prices" (p. 81).

Given the lack of data on CGRPs, it is not surprising that the draft evidence report rates the net benefit of these medicines as "I [Inconclusive]". However, as the data concerns raised in this section illustrate, such a rating is nothing more than a result of these medicines' stage of development.

2. The draft evidence report assumes that "the treatments had no impact on mortality rates" (p. 60). Contradicting this assumption, large numbers of studies have linked migraine to increased health risks.

For instance, migraine has been linked to higher risks of dying from heart problems and strokes. Covering this issue in 2016, a report in the Telegraph summarized the findings from "a team of German and U.S. researchers [who] followed more than 115,000 women aged between 25 and 42 for more than 10 years. They found those who suffered migraines were 50 percent more likely to die during the period."

According to the National Migraine Association, "migraine can induce a host of serious physical conditions: strokes, aneurysms, permanent visual loss, severe dental problems, coma and even death." The National Migraine Association further notes that,

> according to the New England Journal of Medicine, "migraine can sometimes lead to ischemic stroke and stroke can sometimes be aggravated by or associated with the development of migraine." Twenty-seven percent of all strokes suffered by persons under the age of 45 are caused by Migraine. Stroke is the third leading cause of death in this country. In addition, twenty-five percent of all incidents of cerebral infarction were associated with Migraines, according to the Mayo clinic. Most recently the British Medical Journal reported that after evaluating 14 major Migraine & stroke studies in the U.S. and Canada that Migraineurs are 2.2 times greater risk for stroke than the non-migraine population. That risk goes up to a staggering 8 times more stroke risk for women Migraineurs on the pill!

Given the mortality risks associated with migraine, the assumption that CGRP inhibitors, which based on early indications may control migraines better, will not reduce the risk of death is assuming away a very important potential benefit. The draft evidence report should instead incorporate an estimate of the benefits in terms of reduced mortality risk from better controlling migraine.

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3. The draft evidence report does not incorporate the potential impact of CGRP inhibitors on depression and, consequently, fails to consider a significant potential benefit of the drugs.

Depression is a common comorbidity of chronic migraine. Studies indicate that up to 80 percent of chronic migraine patients exhibit the symptoms of depression. Further, depression is associated with worsened migraine-related disabilities and reduced patients' quality of life. Depression is also an important risk-factor for suicide. Through improvements in the number and severity of migraine symptoms, CGRP inhibitors may also help patients' depression symptoms.

Study results summarized in a poster prepared for *The American Academy of Neurology 2018 Annual Meeting* (P4.097: "Efficacy of Fremanezumab in Patients with Chronic Migraine and Comorbid Moderate to Moderately Severe Depression") were consistent with this potential

benefit. Specifically, the study found that patients treated with fremanezumab "experienced significant reductions in the monthly average number of headache days of at least moderate severity and migraine days, with effects observed by Week 4." Further, "patients with moderate to moderately severe depression treated with fremanezumab also showed improved patient-reported outcomes on level of depressive symptomology."

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4. Despite recognizing that CGRP inhibitors have the potential to reduce the costs associated with the opioid crisis, the draft evidence report does not attempt to incorporate the potential benefit into the analysis.

Due to a lack of current effective treatment options, some patients with migraines are prescribed opioids for their headache pain despite the well documented problem of opioid abuse. In 2015 alone, over 33,000 Americans died due to opioid overdoses. The economic cost created by opioid abuse is also large – according to Altarum (a nonprofit health systems research and consulting organization) the total economic costs of the opioid crisis have exceeded $1 trillion since 2001.

It is, consequently, logical to expect that medicines that reduce the need for opioid prescriptions will help reduce these costs. The draft evidence report concurs with this possibility stating that "although data are lacking on the long-term impact of CGRP inhibitors on opioid use and addiction, preventive migraine therapies that reduce the number of migraines and acute medication use may also reduce opioid dependence in this population."

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5. The draft evidence report also violates basic reporting standards – which is particularly relevant if these results are meant to influence actual pricing decisions. Specifically, according to the report (emphasis added), "The treatment effects for each of the medications used in the base-case analyses are listed in Tables 4.4 and 4.5, with *those for the CGRP inhibitors redacted in the tables and text since they were submitted as academic-in-confidence data to ICER* by the respective manufacturers."

Redacting the data on "mean reduction in migraine days" is troubling. The reduction in migraine days is a fundamental benefit that CGRP inhibitors provide patients, and releasing this data helps readers better understand the benefit analysis ICER performed. Releasing the data also helps ensure that other academics and analysts have the necessary information to reproduce ICER's results. Replicability is a core tenet of sound scientific analysis.

Conclusions

The Institute for Patient Access has reservations regarding the conclusions of the draft evidence report on CGRP inhibitors and its potentially negative impact on patient access to these important medicines. We encourage ICER to amend the draft report to reflect the considerations raised in this letter.

If IfPA can provide further detail or aid the Institute for Clinical and Economic Review in incorporating any of the above recommendations into its final draft, please contact us at 202-499-4114.

Sincerely,

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Executive Director

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