

VIA Electronic Mail

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RE: Comments submitted during the Public Comment Period: “Treatments for Acute Migraine”

Dear Dr. Pearson:

On behalf of Allergan plc, the manufacturer of ubrogepant, we are submitting this letter during the Public Comment Period. Our aim is to provide important context and information for consideration in your refinement of the Draft Scoping Document. In March 2019, the U.S. Food and Drug Administration (FDA) accepted Allergan’s New Drug Application for ubrogepant, an orally-administered, small molecule calcitonin gene-related peptide (CGRP) receptor antagonist for the acute treatment of migraine. Its anti-CGRP mechanism of action (MOA) differs from serotonergic and vasoconstrictive triptans and anti-nociceptive opioids by blocking CGRP signaling and binding to the receptor, offering a unique benefit beyond current migraine-specific acute treatments with demonstrated efficacy and absence of vasoconstrictive effects. Ubrogapant’s efficacy, safety, and tolerability have been established in the most rigorous development program that includes multiple clinical trials for the acute treatment of migraine.¹⁻⁴

Comment 1: Multiple endpoints should be included in the comparative effectiveness and cost effectiveness analyses to fully measure the benefits of treatment.

The Draft Scoping Document appropriately identifies multiple efficacy endpoints (i.e., pain freedom and pain relief at 2 hours, sustained pain freedom/pain relief at 2-24 hours and 2-48 hours) that should all be included to capture the benefits of treatment. Importantly, achieving pain freedom or pain relief is a continuous process requiring the use of time to event measures to appropriately capture the full benefits of treatment. Moreover, it is critical to include the time to achieve pain freedom or pain relief beyond the primary time point of 2 hours because an important goal of treatment is to reduce the overall duration of the migraine attack, even in patients without a pain response at 2 hours. Failure to account for differences in the time spent in pain among patients without a pain response at 2 hours will undervalue an important potential benefit of treatment for these patients.

Comment 2: All-cause discontinuation should be considered in the comparative effectiveness and cost effectiveness analyses due to differences in treatment persistence.

High discontinuation rates for triptans have been reported in the literature, as detailed in Allergan’s letter to ICER submitted during the Open Input Period.^{5,6} Data related to discontinuation rates for all emerging treatments under consideration are currently available, and long-term studies revealed differences in

treatment persistence and in reasons for discontinuation.⁷⁻⁹ Inclusion of all-cause discontinuation in the comparative value analyses will ensure the most meaningful and comprehensive assessment.

Comment 3: The comparative effectiveness and cost effectiveness analyses should include all treatment-emergent adverse events or specific adverse events, instead of being limited to serious adverse events only.

Limiting the economic analysis to serious adverse events only will miss important and meaningful differences in tolerability and treatment-related disutilities. This is particularly relevant to the present review given that migraine is a symptomatic condition, and the goal of acute treatment is to control the symptoms without incurring hard-to-tolerate side effects. Published NMAs of existing treatments reported that serious adverse events are relatively rare and reported no statistically significant differences in the occurrence of serious adverse events between most existing treatments and placebo,^{10,11} but reported some statistically significant differences in treatment-emergent and/or treatment-related adverse events compared with placebo.¹⁰ Published cost-effectiveness and quality of life studies have reported costs and disutilities for non-serious adverse events;¹²⁻¹⁵ examples have been included in Allergan's letter submitted to ICER during the Open Input Period. The impact of treatment-emergent adverse or specific adverse events on health-related quality of life is significant and should be accounted for in the comparative value analyses to ensure that benefits of emerging treatments are appropriately considered.

Comment 4: The value-based price and comparative value of the emerging treatments under investigation should be evaluated in patients with unmet need (subpopulation 2 in the Draft Scoping Document).

Currently available acute prescription treatments for migraine (such as triptans and NSAIDs) do not adequately meet the needs for patients with insufficient response to these treatments and for patients with underlying cardiovascular disease or risk factors.^{16,17} The anticipated place in therapy for emerging treatments is in this population with unmet need; therefore, the value of emerging treatments under investigation should be based on this patient population.

Comment 5: ICER should identify the use of opioids for acute treatment of migraine as a low-value service to be reduced or eliminated.

High opioid use among patients receiving acute treatment for migraine attacks has been observed in real-world evidence,⁶ including among patients with insufficient response to triptans¹⁸ and patients with cardiovascular disease or risk factors.¹⁹ Opioids should be excluded from consideration as a potential comparator in the clinical evidence review because opioids are universally discouraged by the guidelines for the acute treatment of migraine in the United States.²⁰⁻²² ICER should use this opportunity to increase focus on reducing the use of opioids for this condition.

Comment 6: Assumptions regarding second dose and rescue medication in the economic analysis should be consistent and supported by evidence.

In real-world use, patients may take a second dose of medication, or an alternate acute medication, to treat persistent migraine that does not initially respond to medication or recurrence of migraine after an

initial response to medication. However, the clinical trials for the emerging treatments under investigation differed with respect to whether or not patients were permitted to take a second dose of study medication or other patient-selected acute medication to treat persistent or recurrent migraine.²³⁻²⁸ In addition, there are limited trial data regarding the efficacy of second dose or rescue medication of existing treatments for persistent or recurrent migraine.²⁹⁻³² ICER should ensure that assumptions regarding the efficacy of a second dose or other rescue medication used in the economic model are consistent and supported by evidence to mitigate possible bias resulting from differences in available evidence.

Comment 7: The economic analysis should include the costs and harms of medication overuse headache (MOH) due to differences in the risk of MOH among acute treatments.

Currently available acute treatments of migraine are receptor agonists (e.g., NSAIDs, ergotamine, triptans, and opioids) which may lead to MOH when used frequently.³³⁻³⁷ By comparison, frequent use of CGRP receptor antagonists may lead to a decrease in the frequency or severity of migraine attacks and do not appear to result in MOH.^{7,33,37-40} Failure to account for differences in the risk and cost of MOH in the economic analysis will miss possible benefits of acute CGRP receptor antagonist treatments.

Comment 8: ICER’s assessment should include real-world evidence demonstrating efficacy of existing acute treatments of migraine are reduced in practice due to medication delay and avoidance.

The efficacy of existing treatments is reduced in practice because 2/3 of patients delay or avoid taking medication due to concerns about adverse events.⁴¹ Delaying or avoiding medication may result in more severe pain, extended headache duration, and increased disruption of work and social activities.^{41,42} These studies indicate that the efficacy of existing treatments demonstrated in RCTs is not representative of the efficacy experienced by migraine patients in real-world use, which should be acknowledged within other potential benefits and considerations.

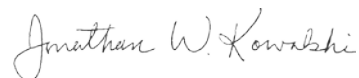
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We appreciate the opportunity to engage with ICER and look forward to a continued dialogue for the review of “Treatment for Acute Migraine.” If you have any questions please contact Priti Jhingran, PhD, Executive Director – US Health Outcomes and Value via e-mail at Priti.Jhingran@allergan.com or Jonathan Kowalski, PharmD, Vice President – US Health Outcomes and Value via e-mail at Jonathan.Kowalski@allergan.com.

Regards,



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Biohaven Commentary on Key Elements of ICER Draft Scoping Document

Biohaven welcomes the opportunity to provide commentary with regard to the ICER Draft Scoping Document and is appreciative of ICER's proviso that all relevant stakeholders are invited to do so. Below we provide our specific responses to key elements of the scoping document, as described by ICER (in quoted italics) below. These include, 1) the overall proposed scope of the Clinical Evidence Review, 2) the general analytic framework for assessment of therapies for acute migraine, (population, intervention, comparators, outcomes, timing, and settings), 3) potential other benefits and contextual considerations, 4) Scope of the Comparative Value Analyses, and 5) Identification of Low Value Services.

1) Proposed Scope of the Clinical Evidence Review

Biohaven agrees with the overall proposed scope of evidence generation. In addition to the data sources from which such evidence will be derived (i.e. comparator trials), we do request inclusion of results from single arm long-term open label safety studies such as Biohaven's BHV-3000-201. Biohaven has presented compelling data from this study with more than 105,000 doses across 1,780 patients with flexible dosing (every other day or as needed) that illustrate the sustained safety of Rimegepant out to 1 year (917 patients to date).¹

2) General Analytic Framework for Assessment of Therapies for Acute Migraine

Populations

"The population of focus for this review will be adults ages 18 years and older with a diagnosis of migraine that is not considered to be chronic (<15 headache days per month...)"

Biohaven maintains that it is important to include patients with ≥ 15 headache days per month w/wo aura. In real world clinical practice, patients with chronic migraine continue to experience acute attacks at a significant monthly rate which must be treated with acute agents.^{2,3} In our phase 3 Zydis® ODT (Oral Disintegrating Tablet) study (BHV-3000-303), approximately 15% of subjects in both the Rimegepant and placebo groups were also taking concomitant preventive medications.⁴ Acute efficacy response in this subgroup was similar to the overall population, and results favored Rimegepant regardless of concomitant preventive medication use. Further, Biohaven has observed effective concomitant use of Rimegepant in acute migraine treatment in case analyses of two patients on CGRP mAb preventive treatment who experienced multiple acute migraine breakthrough events that were effectively treated with Rimegepant.⁵ Biohaven thus maintains that limiting the scope of the evidence review to < 15 headache days per month could inappropriately restrict the population eligible for new acute treatments.⁶ Patients with chronic migraine need effective and safe acute treatment options and currently use agents that were not specifically studied in migraine. Omitting chronic migraine patients could impact the reliability of the proposed budget impact analysis. Lastly, triptans all have broad label indications for acute treatment without regard to migraine frequency and the new products will likely be similarly labeled. It is thus feasible for ICER to include the chronic migraine population and still properly estimate the single dose efficacy and safety outcomes for resolution of the acute migraine attack.

Indeed, for the ICER migraine prevention review, the models "included estimates of the daily costs of acute migraine treatments and other health care services used to treat migraines as well as AEs from the underlying treatments in each of the health states."⁷ Biohaven's long-term safety study (BHV-3000-201) reported 48.4% of patients experiencing a 50% reduction in headache frequency from baseline signaling a likely propensity to reduce the risk for Medication Overuse Headache (MOH).¹ Results were consistent regardless of whether subjects had < 14 or ≥ 14 migraine days during the observation period. It should

further be noted that other CEAs of acute treatment for migraine^{8,9} do not restrict the population to non-chronic-migraine patients.

“We will plan to evaluate two sub-populations of patients with migraine:

- 1. Patients who have attacks that have not responded to non-prescription medicines.*
- 2. Patients who have attacks that have not responded to non-prescription medicines and for whom triptans have not been effective, are not tolerated, or are contraindicated.”*

Sub-population 1 are patients who have found non-prescription medicines to be ineffective or intolerable. Biohaven maintains that there is another segment of sub-population 1: patients that have tried triptans and found them to be ineffective/intolerable, but may then resort to non-prescriptions medications which are eventually deemed to be ineffective. This is supported by evidence from the literature that describes frequent use of oral triptans and NSAIDs in various combinations and sequences. For example, patients with migraine identified from a claims database¹⁰ were surveyed for their use of oral triptans and NSAIDs during their last attack. Among 1,502 surveyed, 64% reported use of NSAIDs followed by oral triptans, 23% reported use of triptans followed by NSAIDs, and 11% reported concurrent use of NSAIDs and Triptans. This study thus suggests that a sizable percentage of this population may have previously used triptans and found them to be ineffective or intolerable. Triptans may therefore not always be relevant as a primary comparator for some patients in sub-population 1.

Sub-population 2 are clearly triptan refractory, intolerant, or contraindicated. We assume that ICER considers these patients to have first tried non-prescription medications and found them to be ineffective. In sizing this population, Biohaven requests that ICER consider CV risks associated with triptan use as an important factor. Biohaven previously provided epidemiologic evidence to ICER suggesting that the combined population of patients with CV disease and others with 3 or more CV risk factors is sizeable (7.7m patients).¹¹ With the availability of safer alternatives, the size of the triptan population deemed to be ineligible may expand. Further, triptan cycling increases risk for Medication Overuse Headache¹² and risk for transition to Chronic Migraine.¹³ Also, triptan non-response is associated with higher rates of depression.¹⁴

Interventions

“.....The full list of interventions is as follows: Lasmiditan, Rimegepant, Ubrogapant”

Biohaven concurs.

Comparators

As stated, it is assumed that sub population 1 patients are eligible for triptan initiation thus mandating comparison between triptans and Rimegepant, Ubrogapant, and Lasmiditan. As noted previously, A sizeable percentage (23%) of such patients may have first used triptans and found them to be ineffective or intolerable, and then tried non-prescription medications that were eventually ineffective .^{15,16} Perhaps such patients should be considered for subgroup analysis as a segment of subpopulation 2. Biohaven further maintains that it is essential to consider all newer trials wherein a triptan arm was included, as these might better capture recent triptan performance.^{17,18,19,20}

The outcomes of interest.....

Biohaven supports ICER’s list of efficacy, safety and patient reported outcomes. Recently, *The Lancet* published the results of our Phase 3 Zydis® ODT single dose study (BHV-3000-303) demonstrating significant improvement versus placebo on 21 pre-specified hierarchical endpoints,²¹ including those selected by ICER, and endpoints demonstrating benefit prior to 2 hours postdose. Biohaven also endorses outcomes that address the durability of response such as pain freedom at 24 and 48 hours, since sustainability of effect might reduce the risk for MOH. Biohaven further maintains that it is important to specify Treatment Emergent Adverse Events (TEAEs), since these might also provide meaningful differentiation between the considered agents. Thus, Rimegepant,¹ Lasmiditan²² and Ubrogapant²³ long-term safety studies should be included in the assessment of safety outcomes. Of note, the Lasmiditan long term safety study reported elevated (>5%) rates of somnolence (8.5%), paresthesia (6.8%), fatigue (5.5%)

and dizziness (18.6%). Also, it has been reported recently²⁴ that Lasmiditan was associated with dose dependent impaired simulated driving performance at 1.5 hours post dosing which resolved by 8 hours postdose.

3) Potential Other Benefits and Contextual Considerations

Biohaven maintains that Rimegepant Zydys[®] ODT for the acute treatment of migraine demonstrate the meaningful benefits of an easy-to-use single-dose formulation, with early and sustained relief of symptoms, low use of rescue medications, and low rates of adverse events.²¹ We maintain that Rimegepant's ODT formulation can provide assurance to patients that its ready use, absent the need for water (an issue for many patients who experience nausea at the onset of a migraine) effectively blunts the debilitating nature of such an attack, allowing patients to resume work or other related activities with confidence.²⁵

Biohaven endorses the list of other contextual considerations as meaningful to the assessment of the value of the novel interventions. Biohaven has presented compelling data from the long-term safety study of Rimegepant with more than 105,000 doses across 1,780 patients that illustrate the sustained safety of Rimegepant, and long-term benefit in terms of reduced frequency of migraine attacks.¹ Biohaven has also provided ICER with data illustrating and sustained and significant improvements in quality of life and disability/activities of daily living with Rimegepant treatment (data on file).

4) Scope of Comparative Value Analyses

".....we will develop a Markov simulation model to assesscost-effectiveness. The model will have a short cycle length (one day) and time horizon (e.g. two years) due to the relative acuteness of migraine attack onset and resolution...The base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only)"

Biohaven maintains that a two year time horizon may be insufficient to demonstrate the long-term cost effectiveness of the new interventions, since that duration will not fully capture the sequelae of increased risk for MOH with triptans,^{26,27} increased risk for transition to Chronic Migraine²⁸, increased disability with triptan cycling,¹² and potential for increases in CV events.¹¹ Also, NSAIDs, ergot compounds, opioids, and barbiturates may have significant CV, GI,²⁹ and addiction risks³⁰ that are likely to manifest long-term.³¹

Biohaven also requests consideration of indirect costs for the base-case analysis, since these are uniquely significant given the persistent and disabling nature of migraine in a primarily employed population. Bonafedes et al. demonstrated equivalent direct (~\$11k) and indirect (~\$11k) per patient annual costs of migraine (the latter including short term and long term disability costs) that significantly exceeded costs derived from a matched referent population.³² We have also provided ICER with data demonstrating substantive improvements in disability with Rimegepant treatment based on MIDAS scores which could be mapped to health resource use and costs in the ICER CEA (data-on-file).

"In separate analyses, we will explore the potential health system budgetary impact of lasmiditan, rimegepant, and ubrogepant over a five-year time horizon..."

Biohaven supports the use of a five year time horizon since effective acute treatment may confer long-term benefits that provide cost offsets that further illustrate the value of the intervention beyond the acute treatment episode (e.g. reduction in frequency of migraine attacks, reduced risk for MOH, reduced risk for transition to Chronic Migraine, and improved QOL and disability/ADL). Biohaven also re-emphasizes the need to acknowledge the complexity of existing therapies (e.g. Triptan-NSAIDs multicomponent therapy) as influencing the appropriate sizing of the triptan refractory/intolerant segments for budget impact assessment.

5) Identification of Low-Value Services

Biohaven agrees with ICER's regard for the importance of capturing so called low value services. Biohaven maintains that the Rimegepant Zydys[®] ODT formulation provides a unique level of assurance to patients that they may readily return to their daily work and other activities with confidence.

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CHAMP

Coalition For Headache
And Migraine Patients



July 19, 2019

PUBLIC COMMENT FROM CHAMP ON ICER'S DRAFT SCOPING DOCUMENT ON NEW MEDICINES FOR ACUTE TREATMENT OF MIGRAINE ATTACKS

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson:

The Coalition For Headache And Migraine Patients (CHAMP) is writing in response to the Draft Scoping Document (DSD) from ICER. CHAMP is a coalition of 22 patient advocacy organizations, patient opinion leaders and migraine communications companies. CHAMP serves as a convening and organizing entity to unite the headache disease patient advocacy community. CHAMP focuses on enhancing communication, coordination and collaboration for the benefit of people living with headache, migraine and cluster diseases.

Just as we did for ICER's 2018 review of erenumab for the prevention of migraine attacks, we will organize the migraine community to submit individual comments during the next open input period (ending on Dec 6, 2019) in response to the Draft Evidence Report. At this stage, we thought it best to collect and share the below vignettes from those living with migraine to bring a personal element to the important issues that are raised in the letter submitted by the Headache & Migraine Policy Forum (HMPF). We have pulled these quotes from a variety of sources, with permission, and to respect patient privacy, we have limited the individual identification to initials and state.

Triptans Don't Work For Many People With Migraine Disease

I have tried nearly all of the "triptans" (oral and injectable) with nausea/vomiting and tingling hands and feet as unwanted side effects. I cannot tolerate these drugs.

--J.K., Pennsylvania

I have adverse reactions to Triptans, crushing chest pain, as well as, allergies. Diphenhydramine is not a TRUE abortive, but it is all that is left to me.

--R.J., Missouri

The triptans worked fine but caused a tightness in my chest. I had often experienced fast heartbeats and a had a lot of anxiety over it. So the very medication that made the headache go away—sumatriptan—also made me feel as though I was courting heart trouble. I would take it, but eventually the chest tightness became so worrisome to me that my doctor switched me to the second triptan, Maxalt.

--M.B., California

The main problem with the current rescue treatments is that even when they do get rid of the pain they put me to sleep. All of the triptans type medicines do this to me, but they are the only medicine that helps the pain or at least reduces it. Imitrex, Maxalt, Amerge, Relpax, Axert, I have tried all of these. I wake up with a terrible migraine attack, take a triptan and then have to sleep another 4-8 hours because of the medicine. It does not make me functional. Quite the opposite, it seems to reset my day night cycle because I end up waking again in the afternoon or evening and that now feels like morning and I can't return to bed again in only a few hours. It's very very disruptive to any normal schedule at all.

--C.L., Kentucky

I was prescribed Imitrex to take during an attack. Unfortunately for me, I experienced cardiac side effects, and could not take that class of medications.

--M.T., Maine

I have explored every treatment I have been able to find and afford, under the supervision of some of the world's most able and recognized migraine specialist physicians. I have been treated with (among many others), the triptans, ergotamine, Zonisamide, Topamax, Neurontin, NSAIDS, and other pain medications. The side effects of some of these have been nearly as disabling as the chronic migraines they were intended to treat. One medication impaired my memory and cognition so badly I was unable to remember more than a few seconds of conversation, leading to my continued and unknowing repetition of sentences I had said. Another sedated me so deeply that my husband was unable to wake me short of shouting and shaking me vigorously. A third sent me to Stanford Emergency overnight. These were expensive in all aspects of the word. For many who suffer from migraine, existing treatments can be nearly as problematic as the illness itself. In sum, current pharmacology falls short.

--A.P., California

Better Managing Migraine Will Lead To Improvements In Comorbidities

I have comorbidities such as depression, anxiety, movement disorder and sleep disorder. When my migraine attacks are not well under control by abortive meds such as triptans and DHE, which don't do an adequate job of providing any meaningful relief, those comorbidities that are typically under control, rise to the surface and scream for me to pay attention to them, while trying to break the migraine cycle. It's a downward spiral that is incredibly difficult to climb out from under. It's a fight every day.

--K.G., California

Migraine also has many comorbidities. I have IBS, anxiety, and depression. My whole life has been impacted. Leaving my house, which has been modified to meet my migraine needs, presents exposure to the many triggers that make my symptoms even worse. It is like entering a torture chamber.

--A.B., California

On top of the physical symptoms, depression and anxiety which follow this disease with all its ramifications is all too real, as is the constant need to have hope despite endless medical failures and terrible side effects from drugs and treatments.

--S.L., California

The Value Of Reducing Opioid Exposure Must Be Counted

When I get a migraine I have to take a cocktail of ketorolac/toradol injection, oxycodone, and Zofran with bed rest. When the migraine doesn't stop, I have to go on a prednisone taper to break it since I have maxed out on the other drugs. Since I've been taking ketorolac frequently, my kidney function has reduced and at one point I had to see a nephrologist. For me, oxycodone helps stop the migraine when taken in conjunction with ketorolac. [sic] I have a very high resistance to pain medication now.

--S.L., California

I was referred to a neurologist at the Mayo Clinic in Rochester, MN. I was seen there and told that I [sic] would benefit from their three-week Chronic Pain Clinic. I attended that program and had some relief from my headaches if I followed the program all day long every day, which doesn't leave much time to have a normal life. The one benefit of the program was getting off opioids, which is a good thing, but I don't have anything to replace it with.

--S.W., Texas

Desperate for relief from migraine attacks, I turned to a pain specialist to explore opioid therapy. Over the course of a year I tried hydromorphone, butrans patches, and methadone, maxing out dosages of all of them. All these opioids made me feel strung out. I was thankful that the pain would go down for a few hours, but then I would always need another dose. I had become chemically dependent and it was negatively affecting my moods and emotions. I felt like a zombie and my relationships were suffering. I made the heartbreaking decision to quit opioids and return to my migraine pain.

-D.V., Arizona

New therapeutic options in migraine are desperately needed and CHAMP asks that ICER's model fully account for all the benefits that new therapeutic options bring to this disease. Thank you for your consideration of the anecdotes from people living with pain who need new options to treat their attacks. CHAMP will continue to engage with ICER throughout this review to ensure that the patient perspective is effectively heard and valued.

Sincerely,

Kevin Lenaburg
Executive Director, Coalition For Headache And Migraine Patients (CHAMP)
HeadacheMigraine.org



Eli Lilly and Company
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U.S.A.
www.lilly.com

July 19, 2019

RE: Lilly Response to ICER’s Draft Scoping Document on Acute Treatments for Migraine

The three key points that Eli Lilly and Company would like to emphasize are that 1) in real world usage, the population likely to receive an emerging novel acute treatment for migraine such as lasmiditan are a subset of the larger population of patients with migraine—that is, patients who are contraindicated to or fail to tolerate or respond to oral triptans. As such, 2) triptans are not an appropriate comparator to lasmiditan. Finally, 3) lasmiditan has a novel mechanism of action relative to the oral calcitonin gene-related peptide (CGRP) antagonists and to the triptans.

General

While the title states that ICER will review “Acute Treatments for Migraine,” there are several references throughout the document to “treatment of acute migraine,” “therapies to treat acute migraine,” “medications for acute migraine,” etc. Note that the word “acute” is appropriately used in this context as a mode of treatment and not a disease subtype. Please modify the language to reflect the appropriate terminology (e.g., “acute treatments of migraine,” “therapies to treat migraine attacks,” “acute medications/therapies for migraine,” etc.).

Background

In paragraph 2, the concept of “specific migraine medications” is introduced, yet it is followed by discussion of opioids and barbiturates, which are not migraine specific treatments. Per the American Headache Society (AHS) Consensus Statement, acute treatments for migraine with established efficacy include triptans, ergotamine derivatives, nonsteroidal anti-inflammatory drugs (NSAIDs) (aspirin, diclofenac, ibuprofen, naproxen), the opioid butorphanol (use is not recommended), and combination medications (AHS, 2019). Barbiturates and opioids are not “specific migraine medications” and should not be listed in this section. A new section titled “Other Commonly Used Medications for Acute Treatment” could be inserted with the statement that these include barbiturates and opioids which are used despite limited evidence of their efficacy, risk for misuse, dependence and overuse.

It should be noted that inadequate management of migraine attacks can lead to increasing migraine attack frequency, which, in turn, can lead to medication overuse headache or chronification of migraine (Lipton, 2013; Lipton, 2015).

It is important to clarify that lasmiditan is the first and only treatment under review by the Food and Drug Administration (FDA) in a new class of medications for the acute treatment of migraine with and without aura. Lasmiditan, which has highly selective affinity for the 5-HT_{1F} receptor, works by decreasing neuropeptide release and inhibiting pain pathways, including the trigeminal nerve (Ramadan, 2003; Labastida-Ramírez, 2017). As currently written, it is not made clear that

lasmiditan represents a distinct mechanism of action and is a separate drug class from the oral CGRP receptor antagonists (oCGRPs).

Populations

In the real world, the population in which lasmiditan will be used is likely to be a small subset of patients with migraine. Sub-population 1 is, therefore, inappropriate and could lead to erroneous overestimation of the budget impact to the healthcare system. A recent survey estimates that 35.1% of adults with migraine are contraindicated to triptans or have failed to respond to or tolerate an oral triptan (Lipton, 2019).

Interventions

Lasmiditan represents a new drug class that is distinct from the oCGRPs. Please list rimegepant and ubrogepant separately from lasmiditan so that the assessment is not erroneously interpreted as a class review.

Comparators

The difficulties in this section will be addressed if ICER focuses exclusively on the correct population: the group that is currently being called “sub-population 2.” Sub-population 1 is erroneous not only for the reasons stated above but also because the proposed comparators for sub-population 1 are not appropriate for lasmiditan.

Triptans are not effective for or not tolerated by all patients, and carry warnings and precautions for patients with risk of cardiovascular disease due to the potential for arterial vasoconstriction (Dodick, 2004). Because of lasmiditan’s high affinity for 5-HT_{1F} and lack of significant pharmacological activity at 5-HT_{1B} or 5-HT_{1D} receptors, it is not associated with vasoconstriction, and therefore, may be appropriate to use in those people with migraine who are unable to take oral triptans due to cardiovascular contraindications (Rubio-Beltrán, 2018).

Commonly used acute therapies for migraine such as NSAIDs, ergot compounds, opioids, and barbiturates are also not appropriate comparators for lasmiditan. In particular, NSAIDs and other over-the-counter medications are recommended as first-line treatment, and migraine patients receiving prescription medications would need to have responded poorly to such treatments or have more severe migraine pain and associated symptoms (AHS, 2019). Additionally, opioids have been shown to reduce responsiveness to other migraine acute treatments, including triptans (Friedman, 2017), and data suggest that the use of opioids and barbiturates may also increase the risk of migraine progression (Bigal, 2009). Therefore, it is recommended that opioid use be reserved for the small subset of patients with severe attacks and a history of nonresponse or variable response to acute treatment (AHS, 2019).

Outcomes

We recommend care in assessing use of rescue medication. A design feature of the phase 3 studies of lasmiditan was an investigation of the efficacy of second dosing. A combined analysis of the studies found no clear evidence that lasmiditan is effective when taken for rescue—that is, for patients who did not achieve headache pain-free status at 2 hours, completed the 2-hour assessments, and took a second dose of study drug between 2 and 24 hours following the first dose (Loo, 2019). Using the rate of second dosing observed in the phase 3 studies would erroneously inflate the cost per episode.

Potential Other Benefits and Contextual Considerations

“This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.”

- Lasmiditan has a distinct and unique chemical structure and pharmacologic profile compared to triptans (Rubio-Beltran, 2018).
- In a clinical trial (SAMURAI) that had 77.9% of participants with at least 1 cardiovascular risk factor in addition to migraine, significantly more patients ($P<0.001$) taking lasmiditan were free from headache pain and their most bothersome migraine symptoms at 2 hours after dosing relative to placebo (Kuca, 2018).
- In a pooled analysis of the SPARTAN and SAMURAI trials, patients taking lasmiditan experienced higher rates of pain freedom than patients receiving placebo, regardless of prior response to triptans. In particular, among patients who identified themselves as poor or nonresponders to triptans, significantly more patients were pain-free at 2 hours with lasmiditan than with placebo (Knievel, 2018).

“This intervention will have a significant impact on improving return to work and/or overall productivity.”

- Migraine patients may perform their job duties less productively while experiencing migraine (presenteeism), regularly stop showing up for work (absenteeism), or leave the workforce or college, which represents a substantial economic impact from a societal perspective (Porter, 2018; Stewart, 2008).
- The Migraine Disability Assessment (MIDAS) questionnaire was administered in a 12-month open-label long-term study (GLADIATOR) at baseline and at months 3, 6, 9, and 12. The results showed significant reduction in total MIDAS score, headache days, and headache pain following lasmiditan therapy (Lipton, 2018).

“This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.”

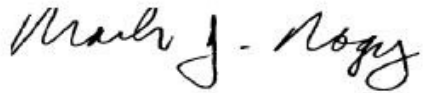
- Migraine typically persists over many years and represents a long-term burden for patients and their families, friends, and colleagues. Migraine is also associated with substantial decreases in functioning and productivity, which, in turn, translates to diminished quality of life for individuals (Hazard, 2009).
- Patients experiencing chronic migraine may also report increased non-headache pain, fatigue, psychiatric disorders (e.g., depression, anxiety), gastrointestinal complaints, and other conditions associated with a long history with migraine pain (Aurora, 2017).

Comparative Value Analyses

ICER plans to model the episodic migraine population only, but we anticipate that lasmiditan will be used to treat migraine attacks across a spectrum of disease, including patients with chronic migraine (>15 headache days/month). All patients with migraine, regardless of whether they have episodic or chronic migraine, and whether or not they are on a preventive treatment, require acute treatment for their migraine attacks.

We appreciate the opportunity to provide comments for this assessment. We feel that consideration should be given to the points we have made to ensure a scientifically sound assessment.

Sincerely,

A handwritten signature in black ink that reads "Mark J. Nagy". The signature is written in a cursive style with a large, stylized initial "M".

Mark J. Nagy
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July 19, 2019

Submitted electronically to: publiccomments@icer-review.org

Steven D. Pearson, MD, President
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Dear Dr. Pearson:

The Headache and Migraine Policy Forum (HMPF) appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) Draft Scoping Document (DSD) on therapies for migraine prevention. The Headache and Migraine Policy Forum is a group of diverse patient advocates who seek to advance public policies and practices that promote accelerated innovation and improved treatments for headache and migraine patients. As the second leading cause of all global disability and the second leading cause of all neurological burden, migraine is a serious public health problem affecting approximately 47 million Americans, 3 million of whom experience migraine attacks 15 or more days per month.¹ There exists an urgent need for improved therapeutic treatment options.

We appreciate ICER's intent to seek multi-stakeholder input as part of its process to assess the value and effectiveness of different migraine therapies. We note that naming the assessment "Treatments for Acute Migraine" does not accurately reflect the content of this review; ICER should instead consider using the proper lexicon for this assessment: "Innovative Acute Treatments for Migraine Attacks."

HMPF encourages ICER to reflect upon the following:

Use of QALY Leads to Insufficient Consideration of the Patient Definition of Value.

Once again, HMPF does not support the use of QALY as a methodology for a value assessment that is meaningful to a patient population that is highly heterogeneous and where the experience of the disease exists on more of a spectrum than other chronic diseases. For persons with migraine and other disabling diseases there is a delicate balance between quality and quantity of life, where poor management of the disease can lead to further chronification and therefore cost. The use of QALY can be discriminatory within the disability community as it treats all patients the same in terms of their condition and value is assessed based on a patient population rather than on an individual. For individuals living with migraine, the return on investment from more time with loved ones, a higher quality of life, and increased productivity in both work and home life has great worth. HMPF respectfully requests that ICER utilize a more patient-centered approach that assigns value to endpoints that represent shorter, incremental gains that may be more meaningful to patients.

ICER Should Fully Consider the Indirect Costs and Societal Burden of Migraine Disease.

The DSD notes that ICER “encourages comments to refine our understanding of the clinical effectiveness and value of treatments.”ⁱⁱ We are encouraged that 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 – but remain concerned that the framework will not adequately address the immense indirect costs and societal burden of migraine. Direct costs are far exceeded by indirect costs to employers including missed work and presenteeism (loss of productivity)ⁱⁱⁱ, exacerbated by the fact that migraine prevalence occurs during the most productive work years (ages 30-49)^{iv}. Patients with migraine also had indirect costs that were \$2,350 higher than those of patients without migraine (\$11,294 vs \$8945), largely attributed to the fact that patients with migraine miss almost 9 more days of work each year than their counterparts without migraine.¹

Related, the lack of acute treatment options also has a specific and negative impact on the wage gap for women. Women are almost half of the workforce, the sole or co-breadwinner in half of American families with children, and receive more college and graduate degrees than men. Yet, on average, women continue to earn considerably less. In 2017, female full-time, year-round workers made only 80.5 cents for every dollar earned by men, a gender wage gap of 20 percent.^v Devaluing acute treatment options for migraine patients – of which 75% are women - further exacerbates the wage gap, particularly since migraine prevalence occurs during the most productive work years (ages 30-49)^{vi} for many female patients already experiencing a wage gap.

Likewise, according to a study published last year on costs associated with migraine disease patients with migraine disease were found to be almost *twice as likely* as patients without migraine to have a short-term disability claim (95% CI, 1.83-2.05; $P < .01$).^{vii} However, patients with migraine who received either acute or preventive medications (odds ratio [OR], 0.81; 95% CI, 0.72-0.91; $P < .01$) or *both* acute and preventive medications (OR, 0.93; 95% CI, 0.89-0.98; $P < .01$) were significantly less likely than untreated patients to have short-term disability claims during the follow-up period.^{viii} Therefore, having additional acute treatments options available would likely mean fewer short-term disability claims for those patients where other therapies have not otherwise been effective.

ICER’s Analytical Framework Must Address Data Showing Higher Healthcare Costs For Failure of Triptans – Including Risk of Chronification - in Order to Draw Accurate Cost-Effective Conclusions.

As ICER notes, effective and early treatment of migraine can yield significant health benefits for persons living with migraine disease. However, where patients do not have adequate acute treatment options and are unable to properly manage their disease with preventive medications, there is a risk of evolution from episodic to chronic migraine disease (chronification).^{ix} Likewise, where certain patients are contraindicated for triptan use because of severe side effects, cardiovascular disease history, gastrointestinal issues, or co-morbid conditions requiring anti-depressants, alternative acute treatment options must be readily available.

The Draft Scoping Document Should More Adequately Address the Cost Benefits of Improved Management of Co-Morbid Conditions.

It is conservatively estimated that the 4.2 million chronic migraine patients spend more than \$5.2 billion a year—\$1,251 per patient—on treatment of chronic migraine.^x The costs of treating chronic migraine increase sharply with the number of comorbid chronic conditions.^{xi} There is potential for these new

therapies to have a profound effect on the chronic *atypical* form of migraine, vestibular migraine, which has a high prevalence.^{xii}

In some instances, the gains in functioning associated with treating migraine may improve the individual's management of co-morbid conditions.^{xiii} For example, if migraine leads to social isolation and depression, treatment may enhance an individual's success in making lifestyle changes or adhering to other treatment regimens. The benefits to both improved quality of life and reduced health care costs for co-morbidities in these instances should therefore be integrated into ICER's value model.

The Draft Scoping Document Must Fully Consider the Positive Impact and Cost Reductions Innovative Acute Treatments Provide on Opioid Use and Abuse by Migraine Patients.

Currently, opioids account for nearly 10 percent of total medications prescribed to treat chronic migraine.^{xiv}

ICER's most recent migraine therapy value assessment included significant discussion on opioid use and the costs associated with long-term use of opioids as rescue therapies. The current DSD should explicitly indicate whether opioids and their impact on productivity / non-direct costs (rescue therapies) will be included in the model. We also request that ICER factor in costs of treating addiction that develops for a percentage of migraine patients who are prescribed opioids and then become addicted. Understanding that all persons living with migraine disease will need acute treatment at some point – and not everyone will qualify for prevention – there remains a large unmet need of having additional – and non-opioid - acute treatments available for patients to return to a normal way of life. In a country gripped by a massive and devastating opioid crisis, we must appropriately value all new non-opioid pain treatments.

HMPF appreciates the opportunity to provide input during this process. If you have questions, please contact Lindsay Videnieks, Executive Director of The Headache and Migraine Policy Forum, at (202) 299-4310 or Lindsay@headachemigraineforum.org.

Sincerely,

Lindsay Videnieks, JD
Executive Director
The Headache and Migraine Policy Forum

On behalf of:

The Alliance for Balanced Pain Management
The Alliance for Headache Disorders Advocacy
The Alliance for Patient Access
Clusterbusters
The Coalition For Headache and Migraine Patients (CHAMP)
The Daily Migraine
The Danielle Byron Henry Foundation
GoldenGraine.com
Health Union / Migraine.com
Migraine Again
The Migraine Diva
Migraine World Summit
National Headache Foundation

Shoshana Lipson, Patient Advocate & Founder, CGRP & Migraine Community, Migraine Meanderings
U.S. Pain Foundation
World Health Education Foundation

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- ⁱ Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016, *Lancet* 2017 Sep 16; 390(10100): 1211–1259
- ⁱⁱ Acute Treatments for Migraine: Effectiveness and Value, *Available at*: https://icer-review.org/wp-content/uploads/2019/06/ICER_Acute_Migraine_Draft_Scope_062819.pdf
- ⁱⁱⁱ Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016, *Lancet* 2017 Sep 16; 390(10100): 1211–1259
- ^{iv} World Health Organization Fact Sheet, “Headache Disorders” Updated April 2016. *Available at*: <http://www.who.int/mediacentre/factsheets/fs277/en/>
- ^v Institute for Women’s Policy Research, *available at*: <https://iwpr.org/issue/employment-education-economic-change/pay-equity-discrimination/>
- ^{vi} World Health Organization Fact Sheet, “Headache Disorders” Updated April 2016. *Available at*: <http://www.who.int/mediacentre/factsheets/fs277/en/>
- ^{vii} Bonafede M, Sapra S, Shah N, Tepper S, Cappell K, Desai P. Direct and indirect healthcare resource utilization and costs among migraine patients in the United States [published online February 15, 2018]. *Headache*. doi: 10.1111/head.13275.
- ^{viii} Id.
- ^{ix} Gerhardt Pohl, Nancy Njuguna, Tomoko Sugihara, Li Shen Loo, Casey Choong, Anthony Zagar, “Economic Aspects of Establishing Prior Use of Two Oral Triptans Before Starting Novel Acute Treatments for Migraine, 2019.
- ^x Messali A et al. *Headache* 2016; 56:306-322 where a recent study estimated that annual headache-related direct costs for chronic migraine and episodic migraine patients were \$4,943 and \$1,705, respectively. The Mean [standard deviation] total annual cost of headache among people with chronic migraine (\$8243 [\$10,646]) was more than three times that of episodic migraine (\$2649 [\$4634], P < .001). Participants with chronic migraine had significantly greater direct medical costs (\$4943 [\$6382]) and indirect (lost productivity) costs (\$3300 [\$6907]) than did participants with episodic migraine (direct, \$1705 [\$3591]; indirect, \$943 [\$2084]) (P < .001 for each).
- ^{xi} Id. at 10, *Table 5*.
- ^{xii} Murdin L, Schilder AGM. Epidemiology of balance symptoms and disorders in the community: a systematic review. *Otol Neurotol*. 2015 Mar;36(3):387–92.
- ^{xiii} Thorpe, K. Prevalence, Health Care Spending and Comorbidities Associated with Chronic Migraine Patients. Feb 2017 p. 8. Retrieved at: <http://allianceforpatientaccess.org/why-impact-cost-of-chronic-migraine-comorbidities-justify-whole-person-care/>
- ^{xiv} Thorpe, K. Prevalence, Health Care Spending and Comorbidities Associated with Chronic Migraine Patients. Feb 2017. Retrieved at: <http://allianceforpatientaccess.org/why-impact-cost-of-chronic-migraine-comorbidities-justify-whole-person-care/>