Feedback to Pharmac on the Pharmacology and Therapeutics Advisory Committee (PTAC) review of erenumab application on 18 August 2022

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From

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Thank you for reviewing the feedback we gave to PTAC on their assessment of the erenumab application that was made on 19-20 August 2021.

We submitted feedback in April 2022, and this was considered at the PTAC meeting 18 August 2022. The meeting record was published on Pharmac's online application tracker in November 2022 (https://connect.pharmac.govt.nz/apptracker/s/application-public/a102P00000BIw0I/p001702). We were notified of this in December 2022.

We have further concerns, based on the record of the PTAC meeting on 18 August 2022, that we would like to see addressed by Pharmac.

1. Referral to Neurological Advisory Committee

Unacceptable delays in seeking clinical advice for the erenumab application

From the 18 August 2022 PTAC meeting record:

> The Committee **recommended** that Pharmac seek advice from the Neurological Advisory Committee, specifically regarding the use of erenumab for acute/episodic migraine, as well as chronic migraine, and the treatment paradigm for migraine, should erenumab be funded.

However, in the email correspondence with Pharmac on 5 December, it was stated that the Neurological Advisory Committee (NAC) does not have any future meetings confirmed, but there was an anticipation of a meeting in 2023.

We note that the referral to the NAC was done at PTAC's August 2021 meeting, but that erenumab was not considered at the NAC's last recorded meeting in October 2021. Sixteen months on, there is still no indication of when the NAC might meet or why no meetings are scheduled for 2023.

This means that Pharmac's action to refer to the NAC will, at best, cause a delay of 18 months to over 2 years, while the erenumab application is "Seeking Clinical Advice" and at worst, an open-

ended delay. Critics of Pharmac have described this kind of delay as a tactic to reduce drug spending. By not scheduling regular subcommittee meetings, Pharmac is validating this kind of criticism.

Request:

1.1 Provide an explanation as to why NAC has not had a meeting since October 2021 and what is being done to ensure regular subcommittee meetings so that applications referred to special advisory committees can be reviewed in a timely manner.
1.2 Set a date for the meeting of NAC in 2023 as early as possible.
1.3 Please advise us of the next NAC meeting agenda.

The information that Pharmac requires to assess erenumab for the treatment of episodic migraine remains ambiguous.

The published PTAC meeting notes from 19-20 August 2022 state:

> Members acknowledged that there is evidence for use of erenumab in the episodic setting, however *as no further information has become available*, at this point of time did not wish to make a formal recommendation for erenumab for acute/episodic [sic: episodic] migraine. The Committee recommended that Pharmac seek advice from the Neurological Advisory Committee regarding a funding recommendation for both chronic and acute [sic: episodic] migraine indications.

It is not clear from the PTAC meeting notes from August 2021 or 2022 what information PTAC and/or NAC requires to complete its advice to Pharmac concerning erenumab treatment for episodic migraine. It is also not clear what other steps have been taken or are required to be taken to obtain this information.

As the peak patient body in Aotearoa for migraine, we have not been asked to provide further information. We do not know whether the applicant or other migraine and headache specialists have been asked to provide further information. However, we do know that there is information on the treatment of episodic migraine with erenumab and other calcitonin gene-related peptide (CGRP) monoclonal antibodies. Some of this has been published since the erenumab application was received by Pharmac in February 2021 (e.g. the Technology appraisal guidance: Erenumab for preventing migraine, published by the National Institute of Healthcare Excellence (NICE), published in March 2021, www.nice.org.uk/guidance/ta682).

It is not clear to us what process Pharmac takes to ensure new evidence is considered for new drug applications, especially when there is a long delay between the submission of an application and its review by PTAC and other committees.

Request:

1.4 Please explain the process for considering further information related to use of erenumab for episodic and chronic migraine and how this information will be made available to PTAC and NAC.
1.5 Confirm that PTAC and NAC will consider the most current and up to date evidence on erenumab for the treatment of episodic and chronic migraine at its meetings.

Unacceptable process for seeking clinical advice

PTAC has recommended that the erenumab application is reviewed by NAC. However, we note that none of the members of NAC have a stated special interest in migraine or are migraine and headache specialists; and that two members of PTAC, who will have already given their advice as

part of PTAC's consideration, are also members of NAC (Dr Giles Newton-Howes and Professor Brian Anderson). Dr John Mottershead has published articles on headache disorders for a local audience (in New Zealand Doctor and for BPAC), but his stated interest is in multiple sclerosis and to the best of our knowledge he is not a headache specialist.

There is a bias against migraine and headache treatment in New Zealand. PTAC noted this in its August 2021 meeting notes when it considered that people with migraine have limited access to neurology services due to "high demand for neurology services". This is another way of saying that migraine is not prioritised by most treating neurologists - there is a bias against treating migraine and headache in New Zealand.

This bias is manifest in the huge unmet need for health services and treatments for patients with migraine. Worldwide data suggests that patients with headache form the largest referral group to neurology.[1] However, there is a lack of access to better and evidence-based treatments for patients with migraine in New Zealand, a lack of specialist headache clinics and headache specialists, even though migraine and other primary headache disorders are the second leading cause of years lived with disability in the world.[2] People with migraine often describe having had negative, and sometimes stigmatizing, experiences with healthcare professionals.[3] The availability and use of CGRP receptor antagonists may help reduce the extent of unmet need in the treatment of migraine attacks, resulting in more patients receiving treatment, better outcomes for people with migraine, avoidance of hospital admissions and reduction of medication overuse with agents like opiates, which is associated with high disease burden in people with migraine.[4] All of this can lead to direct and indirect cost savings for the government in health care costs, and greater economic productivity as patients with migraine are able to contribute more with effective treatment.[5]

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[1] Ridsdale L, Mtandabari S, Noble A038 Referral patterns to neurology: past, present and future. Journal of Neurology, Neurosurgery & Psychiatry 2012;83:e1.

[2] GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016 Oct 8;388(10053):1545-1602.

[3] Parikh SK, Kempner J, Young WB. Stigma and Migraine: Developing Effective Interventions. Curr Pain Headache Rep. 2021 Dec 6;25(11):75

[4] Schwedt TJ, Buse DC, Argoff CE, Reed ML, Fanning KM, Hussar CR, Adams AM, Lipton RB. Medication Overuse and Headache Burden: Results From the CaMEO Study. Neurol Clin Pract. 2021 Jun;11(3):216-226.

[5] Mallick-Searle T, Moriarty M. Unmet needs in the acute treatment of migraine attacks and the emerging role of calcitonin gene-related peptide receptor antagonists: An integrative review. J Am Assoc Nurse Pract. 2020 Apr 16;33(6):419-428; Varnado OJ, Ye W, Mi X, Burge R, Hall J. Annual indirect costs savings in patients with episodic or chronic migraine: a post-hoc analysis of phase 3 galcanezumab clinical trials in the United States. J Med Econ. 2023 Jan 5:1-15. doi: 10.1080/13696998.2023.2165365.

There is a significant amount of research into the cost-effectiveness of CGRP monoclonal antibodies that is well-known by headache specialists but which general neurologists would be unlikely to be familiar with, including US-based models of cost-effectiveness of erenumab.[6] [7]

Given this context, referring a migraine medication application to a specialist committee that has limited migraine and headache expertise runs the risk of entrenching the bias against migraine disease and jeopardising sound advice. We consider it essential that both the erenumab and the galcanezumab applications are reviewed by neurologists with a special interest in migraine and headache.

Request:

1.6 We ask that migraine and headache specialists are invited to consider the erenumab application at the next NAC meeting and the galcanezumab application whenever this is assigned to a committee for review. We are happy to facilitate this and provide contacts with headache specialists in Aotearoa.

2. Migraine language

The lack of migraine and headache expertise on PTAC is illustrated by the incorrect terminology that PTAC uses in its August 2022 meeting notes on erenumab. They refer to "acute/episodic migraine". This is not a migraine disorder and appears to confound two different aspects of migraine.

As correctly outlined in PTAC's August 2021 meeting notes, migraine is defined as either episodic or chronic:

- a person has "episodic migraine" if they have fewer than 15 migraine days per month, and
- a person has "chronic migraine" if they have 15 or more headache days per month over 3 consecutive months with 8 of those days having migraine features (such as cognitive impairment, dizziness, visual disturbances, lethargy, nausea).

Episodic migraine is further broken down into:

- low frequency episodic migraine (zero to 3 migraine days per month) (LFEM),
- medium frequency episodic migraine (4 to 7 migraine days per month) (MFEM), and
- high frequency episodic migraine (8 or more migraine days per month) (HFEM).

The term "acute migraine" may be used to describe a discrete migraine attack. However, people with both episodic and chronic migraine may have an "acute migraine" attack so it is incorrect to conflate episodic with acute migraine.

The Coalition of Headache and Migraine Patients (CHAMP) has produced a series of language guides to assist people who communicate about migraine and headache to do so in a more informed and accurate way. CHAMP's guides are widely accepted and used internationally and may assist Pharmac and its advisory committees in their considerations of migraine medications. The latest edition can

[6] Sussman M, Benner J, Neumann P, Menzin J. Cost-effectiveness analysis of erenumab for the preventive treatment of episodic and chronic migraine: Results from the US societal and payer perspectives. Cephalalgia. 2018 Sep;38(10):1644-1657

[7] Institute for Clinical and Economic Review (ICER). 2018. Calcitonin gene-related peptide (CGRP) inhibitors as preventive treatments for patients with episodic or chronic migraine: effectiveness and value - final evidence report. ICER, Boston

be found here: https://headachemigraine.org/headache-and-migraine-disease-language-and-image-guide/

Request:

2.1 Please let us know if Pharmac or a committee needs further assistance to understand classifications of migraine.

3. Other Special Advisory Committee referral

The PTAC meeting notes from 19-20 August 2021 indicate that PTAC considered referral of the erenumab consumer funding application to the "Analgesics Subcommittee". We consider this to be unnecessary, leading only to further delay of the application's processing. The CGRP monoclonal antibodies under consideration are not analgesia and have no evidence in acute treatment of migraine. This novel class of medications, as noted above, is used for the prevention of migraine.

Request:

3.1 Please confirm that Pharmac does not intend to refer the erenumab application to the Analgesic Advisory Committee.

4. Galcanezumab for treatment of episodic migraine

We interpreted PTAC's August 2021 meeting notes to mean that Pharmac would not be considering erenumab for the treatment of episodic migraine. However, PTAC's August 2022 meeting notes clarify that PTAC recommended that Pharmac seek advice from the NAC "regarding a funding recommendation for both chronic and acute [sic: episodic] migraine indications."

Had we understood that funding of erenumab for episodic migraine had not been ruled out, we would have included the treatment of episodic migraine in our application for funding for galcanezumab. In particular, Australia has now funded CGRP monoclonal antibodies for people with HFEM in light of studies that have shown that people with HFEM suffer comparable disability to those with chronic migraine. See for example:

- Buse, DC, Reed, ML, Fanning, KM, Bostic, RC and Lipton RB. Demographics, Headache Features, and Comorbidity Profiles in Relation to Headache Frequency in People With Migraine: Results of the American Migraine Prevalence and Prevention (AMPP) Study. Headache. 2020;0:1-17
- Chalmer, MA, Jansen, TF, Lebedeva, ER, et al. Proposed new diagnostic criteria for chronic migraine. Cephalalgia. 2020;40:399-406
- Torres-Ferrus M, Quintana M, Fernandez-Morales J et al. When does chronic migraine strike? A clinical comparison of migraine according to the headache days suffered per month. Cephalagia. 2017;37:104-113
- Ishii, R, Schwedt, TJ, Dumkrieger, G, et al. Chronic versus episodic migraine: The 15-day threshold does not adequately reflect substantial differences in disability across the full spectrum of headache frequency. Headache. 2021; 61: 992– 1003.

Given that erenumab will be considered in the treatment of episodic migraine, we would like galcanezumab to also be considered for this indication.

Request:

4.1 Please inform us of the process to ensure that galcanezumab will also be assessed for treatment of episodic migraine.

5. Process for assessment of galcanezumab consumer funding application

We are concerned that the delay and lack of expertise applied in the assessment of the erenumab application (set out under headings 1 and 3 above) may be repeated in the funding process and assessment for galcanezumab.

Request:

5.1 What assurances can you give us (if any) that the process for assessing galcanezumab will not be subjected to the protracted delays of the erenumab funding application process?

5.2 What assurances can you give us (if any) that should Pharmac require additional advice on galcanezumab, that it will consult with migraine and headache specialists and not only general neurologists or those who specialise in other fields of neurology (Parkinson's, dementia, multiple sclerosis, epilepsy, stroke)?

5.3 Is there anything we can do to ensure the process for galcanezumab stays on track time-wise and involves migraine and headache specialists?

5.4 Could the meeting of NAC in 2023 consider the erenumab and galcanezumab applications together? Both erenumab and galcanezumab are calcitonin gene-related peptide (CGRP) monoclonal antibodies and both are administered in the same manner. This would be an efficient use of committee members' time. It would also mean that our consumer funding application for galcanezumab would be considered in conjunction with the erenumab application. Our application discusses all of the matters that PTAC suggested be reviewed by the NAC ("1.3…where erenumab would be placed in the sequence of migraine treatment; the need for secondary care advice in this patient population; costs of subcutaneous administration and training; and the proposed Special Authority criteria"). It has also been peer reviewed by Dr Pyari Bose (one of New Zealand's few headache specialists) and Professor Debbie Hay (one of New Zealand's few migraine researchers).