Migraine Australia

Submission to the Standing Committee on the Health, Aged Care and Sport: Inquiry into approval processes for new drugs and novel medical technologies in Australia

Prepared by the Research and Advocacy Working Group of Migraine Australia

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1. Introduction

We would like to thank the Committee for holding this inquiry and giving us the opportunity to make a submission on behalf of Australians living with migraine. We hope that by relating the experiences and situation of Migraine Australia and its individual members, the Committee will gain a clearer understanding of the shortcomings and flaws that could lead to negative outcomes inherent in the approval processes for new drugs and novel medical technologies in Australia.

Migraine Australia is a new patient advocacy body representing, supporting and promoting the interests of the 4.9 million Australians who live with migraine. Migraine Australia exists largely because new, very successful[1] medications to manage migraine have faced many difficulties in achieving PBS listing. These medications are Calcitonin Gene Related Peptide (CGRP) antagonist monoclonal antibodies, three of which are currently available in Australia but not yet listed on the PBS: Erenumab (Aimovig), Fremanezumab (Ajovy) and Galcanezumab (Emgality). More information about our organisation can be found at www.migraine.org.au.

This submission tells our story of trying to navigate the new drug approval and listing process before addressing the terms of reference directly. As the terms of reference are relatively technical, we have not encouraged our members to make their own submissions, however, we are happy to provide evidence on request of the impact the delay in new medications has on the lives of people living with migraine.

2. Our story

We would like to share with you our story, because the story of why Migraine Australia exists is inextricably linked with the process of bringing new drugs to the Australian market.

[1] Edvinsson, L, Hannes, KA, Warfvinge, K and Krause, D, 2018, *CGRP as the target of new migraine therapies – successful transition from bench to clinic,* Nature Reviews Neurology, 14(338-350), https://doi.org/10.1038/s41582-018-0003-1

When Aimovig was first released in the United States in 2018, most of the founding members of Migraine Australia had been aware to varying degrees that there were these new drugs overseas that were "purpose built" for migraine and delivering amazing results. The stories people were telling were quite simply unbelievable: we had exhausted all options for years, were told migraine was something we just had to live with… Could this possibly be true? New online groups were formed of people very hungry for information about these new medications.

The CGRP medications seemed to have little trouble going through the Therapeutic Goods Administration (TGA) processes, and Aimovig was available in Australia shortly after it was available in the US. The TGA documentation was clear, accessible, and easy to find on its website.

Our neurologists assured us that it would be just a few months before Aimovig was on the PBS – it had to go through another process with the Pharmaceutical Benefits Advisory Committee (PBAC) first, and we could have it for free in the meantime. This was great! But when we came together as a community to discuss it, we uncovered some very unfair disparities. The number of people allowed on the Patient Familiarisation Program (PFP) was limited to 10 patients per prescribing doctor by Medicines Australia. Our vertical learning curve began: firstly, who were Medicines Australia, and why would they have such an unfair rule that penalises people who have a migraine specialising neurologist? There are only around 70 neurologists who specialise in migraine and headache in Australia, each with a very long list of patients who would benefit from, and qualify for, these new drugs. However, regardless of their specialisation, or patient numbers, they could only put 10 on the PFP. Medicines Australia advised it was a *product* familiarisation program: it was for doctors to get experience with the new drug, and not a way for patients to bypass the PBS system.

'Don't worry' our neurologists said, there's a three-month free trial program that everyone can try, and it will be on the PBS soon.

At the July 2018 meeting of the PBAC, Aimovig was rejected. The Australian public weren't informed until 6 weeks later, and the reason why was not released until 4 months after the

meeting when the frustratingly opaque, uninformative and bureaucratic Public Summary Document (PSD) was published. What organisation takes four months to produce minutes?

'Don't worry' our neurologists said, this happens sometimes, they'll resubmit, it will be listed, everything will be fine.

Meanwhile, the inequity of those on the PFP versus those on the three-month trial of Aimovig became more confronting, as the former enjoyed ongoing free medication, and the latter either had to stop treatment or pay up to $850 a month. Other evidence of discrimination emerged, such as some pharmacies charging 'dispensing fees' of up to $175 for people to get their medication which was being provided for free under the access programs. Some neurologists were also charging exorbitant fees to put people on access programs. So, while some patients were getting the new drugs for free and not being charged extra by their neurologist or pharmacy, others were paying hundreds or even thousands of dollars for the same medication for the same condition.

By early 2019, many of us had made our way onto an Aimovig access program or were thinking about it. We were actively discussing Ajovy and Emgality too, and those who had not done well on Aimovig were impatiently waiting for the new medications to arrive. The second application to the PBAC for Aimovig was scheduled for the March 2019 meeting and many neurologists were confident that it would be listed. However, our founder, Raphaella Kathryn Crosby, noticed a problem. There was a widespread belief that all that was required for PBS listing to happen was the PBAC recommendation, and as soon as that recommendation was delivered it would be a matter of days before it was on the PBS. There was no understanding that it then needed to go to the Department of Health, then to the Minister, and – as these drugs are likely to cost more than $20m each year - to the full Cabinet for approval. Nor that there was a lengthy administrative process to get the medication into the system. With this awareness, she created a petition – a simple one, aligned to the election, asking for both sides of politics to commit to listing the medications when the PBAC recommended them. The petition was both an education tool – to make people aware that the final decision was a political one – and an attempt to get either potential health minister on record saying that they would list the medications. And they did, with the oh-so-familiar line "we will list everything recommended by the independent PBAC".

PBAC did not recommend Aimovig, news that was released just days before the election. Gutted, bewildered, and perplexed as to why a drug so remarkable would not be enthusiastically embraced, we realised we needed to learn more about this very confusing PBAC process.

That original petition wasn't pushed very hard, but it began the movement that is now Migraine Australia. Petition signatories and the members of the CGRP Facebook groups that this movement came from voted for a permanent patient organisation to represent and support people living with migraine. This budding patient advocacy group had not yet held a meeting when Emgality was on the agenda for the PBAC meeting in July 2019; despite this, we managed to rally enough support and encourage people to submit sufficient 'consumer comments' to the Emgality application that made a difference, and Emgality was recommended.

This time our neurologists were not optimistic. There was a condition on the positive recommendation for Emgality stating the new medications should only be provided under the existing risk share agreement, or cap, for onabotulinum toxin A (Botox) for migraine. This cap was already insufficient for the patients receiving Botox, as the PBAC well knew having rejected the attempt to get the cap increased at the March 2018 meeting[2].

This time our neurologists did not say 'don't worry': they knew that the poisoned pill of forcing these new drugs under the existing Botox cap would ensure that the new CGRPs would not be listed on the PBS.

Teva launched a PFP for Ajovy that was over-subscribed in the first six weeks, in part because the offer came with a guarantee of no dispensing fees: Teva organised for medications to be dispensed from a single pharmacy in Gosford and mailed to PFP participants. This was an expensive exercise given the need to maintain cold chain (that is, the medication must remain refrigerated until use), and the system was put under pressure during the 2019-20 bushfires and coronavirus lockdown when Australia Post's service delivery started to

[2] PBAC, Public Summary Document – March 2018 PBAC Meeting: 7.02 Botulinum toxin type A purified neurotoxin complex: Lyophilised powder for injection, 100 units; Botox®
https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2018-03/files/botulinum-toxin-psd-march-2018.pdf

struggle. Lilly opted not to do a PFP for Emgality, but instead offered a discount voucher deal that offered the first two months free, and then a discounted price of $297 a month, instead of $1000. Our nervous neurologists, however, not wanting to put people in an impossible financial position, began turning patients away from the CGRP medications and back to older therapies they knew their patients could afford.

Aimovig was being considered for the third time at the November 2019 PBAC meeting, as well as Ajovy for the first time. This time we at Migraine Australia were ready, but we were still new, and still trusted the system. One problem with the PBAC system is that applications are not made public, and it is very difficult to make a submission on an application when you are not aware of its contents. Despite this, we did our best to put forward a comprehensive argument, including doing surveys and gathering data from everywhere we could. We pushed to get as many people as we could to make their own comments to PBAC, to tell their own stories, and make it clear that there are a lot of people who need this medication to live pain- and symptom-free lives. We had meetings with Jo Watson, the Deputy Chair of the PBAC, to ensure we were giving the committee the desired information. We warned her during those meetings that Novartis would not try again if Aimovig was not recommended this time. She laughed and said, “they always come back”.

In October 2019, Novartis withdrew Aimovig from the agenda of the November PBAC meeting, following a report from the Economic Sub Committee of PBAC that indicated to Novartis that the outcome would be the same as the first two rejections. Novartis were very respectful to Migraine Australia; they briefed our leadership team a couple of days in advance so we could prepare a crisis communication plan and get ready for many of our members to be distraught, and even suicidal, at the news: Aimovig was not going to be listed on the PBS. Possibly ever. We reassured our members that those getting it at no cost on the PFP would continue to do so, (underlining the unfairness of that system), and provided around the clock support to the thousands affected. We are still eternally grateful to Novartis for opting to withdraw so we did not get the devastating news of another PBAC rejection the week before Christmas.

Migraine Australia also did something we are told is unheard of: we publicly supported the actions of the drug company and criticised the PBAC process. It was our view then, and it is

still our view, that the PBAC should have recommended Aimovig. It would appear from reading the PBAC authorising legislation, the *National Health Act (Cth) 1953*, it is not within the PBAC's remit to base a decision for not recommending of a safe, effective, and cost-effective drug based solely on the estimated impact to the budget. Section 101 part 3A of the legislation specifies:

> *For the purpose of deciding whether to recommend to the Minister that a drug or medicinal preparation, or a class of drugs and medicinal preparations, be made available as pharmaceutical benefits under this Part, the Committee shall give consideration to the effectiveness and cost of therapy involving the use of the drug, preparation or class, including by comparing the effectiveness and cost of that therapy with that of alternative therapies, whether or not involving the use of other drugs or preparations.*

The consideration of impact on the health budget appears to be a classic example of mission creep, appearing in section 4.5 of the PBAC guidelines[3], despite not being mentioned in the legislation as a criterion for recommendation or otherwise.

The PBAC found Aimovig to be both clinically effective and cost effective[4], but, as we understand it, the decision to not recommend Aimovig was made solely because the number of patients that would potentially use the medication is too large, and thus listing it would significantly impact the health budget. As we continued along this very steep curve of learning about this odd, opaque system, we quickly appreciated that PBAC is not a fair playing field. This does not appear to be a group of impartial experts assessing clinical benefit. The decision to reject Aimovig twice was not because it doesn't work – it does. It was not rejected twice because it is not cost effective – it is. It was rejected because there are too many migraine patients. The line item in the budget was too big, in their opinion. The

[3] PBAC, Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee, Version 5.0, September 2016, https://pbac.pbs.gov.au/information/printable-version-of-guidelines.html
[4] PBAC, Public Summary Document – March 2019 PBAC Meeting, 7.05 Erenumab: Injection 70 mg in 1 mL single dose pre-filled pen; Aimovig®, https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2019-03/files/erenumab-psd-march-2019.pdf

clinical benefit, and even quality of life benefit, is discarded in the face of limited economic analysis and bias of which diseases are more 'deserving'.

The economic analysis is undoubtably flawed, or at best, easily critiqued. That we are mostly young and otherwise healthy people who could go back to work and pay taxes, more than offsetting the cost of the medications, is not taken into consideration. Medications for the elderly or terminally ill are seemingly waved through, while drugs for the young – whether it be our CGRP drugs or the much-discussed Cystic Fibrosis drug Orkambi – face a significant fight. Most of the analyses on cost and impact of the medications on the PBS budget is blacked out or not released, so we cannot comment on it, let alone know what assumptions have been made about our lives. The very little that we can see, delivered in bureaucratic, confusing Public Summary Documents, does not explain the decision at all, but does provide significant evidence of entrenched stigma against migraine and that the PBAC has a poor understanding of the condition and how it is managed. There is no opportunity in the process for us to give feedback or input on the advice from PBAC in the recommendations – no opportunity to tell PBAC they got something wrong. We note that there has been no wider cost-benefit analysis which examines the potential savings across both State and Federal budgets of many migraine patients being able to return to work.

Subsequent discussion blaming drug companies for the failure to list any CGRP medications on the PBS are perplexing. PBAC chair Professor Wilson said that the drug companies 'got what they requested'[5], which is baffling: no company asks for a scenario where they lose significant amounts of money. Lilly and Teva have already agreed to a heavily discounted Botox equivalent pricing and cost minimisation to try and secure reimbursement, despite these medications being vastly superior to Botox by almost every measure. Novartis have been the most generous and supportive to their patients and bent considerably to try and please PBAC – including changing a very valid claim of superiority over Botox to non-superiority. Emgality and Ajovy have recommendations from PBAC; it is the Minister's responsibility to act on his promise of listing all PBAC recommendations. Instead, despite there obviously being some agreement between Lilly and the Department on Emgality, boxed

[5] BiopharmaDispatch, 2020. 20 July, viewed 20 July 2020, https://pharmadispatch.com/news/pbac-chair-migraine-companies-got-what-they-requested

in by the Minister's own misleading statements that PBAC advice is a "legally binding requirement"[6] we are now enduring an unnecessary six-month delay while Emgality goes back to PBAC.

We have very little confidence that these essential medications will ever be listed. We no longer trust the system. More than 15 months on from the Emgality recommendation, nearly 12 months from Ajovy's recommendation, with neither drug yet listed on the PBS, our doctors have largely given up hope. They are no longer putting people on to trial programs, or chatting excitedly about Vypeti, Nurtec, Ubrelvy or Reyvow - the next batch of new migraine-specific medications that are already available in other countries. There is some indication their respective companies are delaying bringing these new medications to Australia because of the way Aimovig, Emgality and Ajovy have been handled.

The entire community is deflated… and very angry. From the perspective of many in the migraine community, the entire PBAC/PBS process feels like a scam. PBAC makes recommendations, Government says they will list those recommendations, but from our vantage point it appears that both PBAC and Government expect drug companies to effectively give their product away for free, and/or are setting them up to take the blame when medications are not listed. Patients live on tenterhooks believing and trusting that the right thing will be done, drug companies spend millions of dollars bringing their product to market, but the system is rigged. We have tried to get people to rally in support of Emgality's reapplication to PBAC currently underway, but our people no longer trust the system, and don't see the point. Even the persistent use by the PBAC and its members (and the Department, and the Health Minister) of the word 'migraines', despite repeatedly communicating that the name of the disorder is 'migraine' (without the 's'), is perceived as evidence that they are not listening and do not care.

[6] Hunt, G. House of Representatives, speaking to the Therapeutic Goods Amendment (2020 Measures No. 1) Bill 2020 - Second Reading, 17 June 2020, 10.45am, https://www.aph.gov.au/Parliamentary_Business/Hansard/Hansard_Display?bid=chamber/hansardr/4057a488-4d29-49e7-b8e7-52d45368ebe6/&sid=0000

When the Government and government processes like PBAC are failing its citizens, and the 'big bad' drug companies are the only ones on our side, people have a right to be angry. The Standing Committee should be in no doubt that we, the migraine community, are furious.

3. Response to terms of reference

3.1. The range of new drugs and emerging novel medical technologies in development in Australia and globally, including areas of innovation where there is an interface between drugs and novel therapies

New medications have become available in the last two years that can significantly assist in the management of migraine. While these new medications will not eradicate migraine related impairment and disability, they do go a long way to reduce the demand of people living with migraine on the health, welfare, and disability systems by making significant migraine manageable. These are first-in-class medications, the *only* specific medications designed to prevent migraine attacks. However, they have not been listed on the PBS, with a clear signal from the PBAC that they do not believe managing migraine is worthy of taxpayer money. The first of these new medications, erenumab (Aimovig), has been withdrawn from the PBS process by Novartis because of the attitude of the PBAC, after being rejected in July 2018 and March 2019. Galcanezumab (Emgality) was recommended in July 2019 and fremaneznumab (Ajovy) was recommended for listing November 2019, but neither have yet been listed.

The CGRP breakthrough has significantly increased both the understanding of migraine – increasing awareness that migraine not a vascular condition or a headache, but is a complex neurological condition with recurrent attacks – and sharply increased the interest of pharmaceutical companies in developing treatments for migraine. We are no longer being told we 'just have to live with it' or that there is nothing that can be done. The new classes of medication either now in the market or in development that we know of are detailed below.

- Numabs: CGRP antagonist monoclonal antibody treatment that works to prevent migraine attack by blocking the CGRP receptor.
    - Aimovig (Novartis), TGA approved 2018, withdrawn from PBS consideration after two failed attempts)

- Nezumabs: CGRP antagonist monoclonal antibody treatment that works to prevent migraine attack by blocking the CGRP ligand.
    - Emgality (Lilly), currently re-applying to PBAC, was recommended July 2019 but failed to list
    - Ajovy (Teva), recommended by PBAC November 2019 but not yet listed
    - Vyepti (Lundbeck), currently available in the US but not yet in Australia
- Gepants: CGRP antagonist tablet medications that can be taken either as an abortive medication to treat an individual attack, or as a daily dose to prevent migraine attack.
    - Nurtec (Biohaven), currently available in the US as a tablet or dissolving wafer, not yet in Australia
    - Ubrelvy (AbbVie), currently available in the US but not yet in Australia
    - Atogepant (AbbVie), completed Phase 3 trials, due for release early 2021
    - Zavegepant (Biohaven), nasal spray delivery in Phase 3 trials (note: also being investigated as a possible COVID-19 treatment so may be accelerated to market)
- Ditans: serotonin inhibitor targeting the 5-hydroxytryptamine (5-HT 1F) receptor, works similarly to Triptans in aborting migraine attacks but without the vasoconstriction that is a problem for patients with heart conditions.
    - Reyvow (Lilly) currently available in the US but not yet in Australia
- Others in early development/research
    - Lu AG0922 (Lundbeck) is a monoclonal antibody designed to inhibit pituitary adenylate cyclase-activating polypeptide (PACAP) signalling for migraine prevention. PACAP was found to be one of the chemicals that surges during the trigger sequence of migraine attacks, similarly to CGRP.
    - Resveratol, a product derived from berries believed to be of assistance to women with hormonally triggered migraine, is currently in clinical trials being conducted by the University of Newcastle.

Additionally, research is underway at the University of Adelaide and the University of Sydney to develop a diagnostic test, in addition to the world leading genetics research at Queensland University of Technology. The development of a diagnostic test will enable accurate diagnosis of subtype and more targeted, effective treatments being developed.

3.2. Incentives to research, develop and commercialise new drugs and novel medical technologies for conditions where there is an unmet need, in particular orphan, personalised drugs and off-patent that could be repurposed and used to treat new conditions

The incentive to develop new migraine therapies is somewhat obvious: the estimated $US5 billion (and growing rapidly) global market for pharmaceuticals designed for managing migraine[7]. This a market that is currently significantly underserved with many opportunities for new and better treatments. The major disincentive is that there are many gaps in the basic understanding of migraine, particularly migraine aura, making the development of effective new treatments a profoundly expensive exercise. Many of the treatments being clinically trialled for use in treating migraine are anti-inflammatories or analgesics that did not work for their original purpose, so they are trialled for migraine in the misguided hope they will be effective. The lure of a huge underserved and desperate market is too tempting for the bottom end of the therapeutic market.

There is a significant challenge in treating the rarer subtypes of migraine, such as abdominal, brainstem, hemiplegic and vestibular migraine. Abdominal, brainstem and vestibular migraine thus far seem to have less success with CGRP therapies, although they are beneficial for some, while hemiplegic patients are overrepresented among super-responders (more than a 75% improvement in both frequency and severity). But, because medical science is in an early phase of understanding what is going on in a migraine attack, the 'why' behind these particular subtypes and their differences is not well understood. Misdiagnosis is common. Delay in accurate diagnosis and appropriate care is common. And, even with accurate diagnosis and good care, we simply do not know why some people are not responding as well to CGRP therapies, nor what might work better.

[7] Market Data Forecast, Global Migraine Drugs Market Analysis - By Treatment (Preventive & Absorptive), Therapeutic Class (Triptans, Ergots & Others) & By Region - Industry Size, Share, Growth, Trends, & Forecast | 2019 – 2024, February 2020, https://www.marketdataforecast.com/market-reports/migraine-drug-market

These rarer subtypes of migraine are often excluded from clinical trials, and many medications are contraindicated for people with these rarer subtypes because they were excluded from trials. A cost-effective strategy may be to provide funding for a subset of the trial that is happening anyway to include those rarer subtypes.

Prior to the advent of CGRPs in 2018, off-label and repurposed medications was all we had for the prevention of migraine attack. While we have no issue with those treatments being tried, we have significant objection to being forced to try three of them before being able to access CGRP therapy, as is currently proposed for access on the PBS. We do not want to see increasing numbers of older, ineffective drugs with significant side effects being forced on people with migraine. Migraine is a very complex neurological disease, and the hypersensitive nature of migraine brain means that side effects are common and often severe. We need medications that were created specifically for us.

Markets that we feel could be the next source of significant advancement – beyond treating migraine itself – are pain relief and anti-depressant medications specifically made for the hypersensitive migraine brain. We do not know enough yet, but we do know that the migraine brain fundamentally works differently (all the time, not just during attacks) to a neurotypical brain[8]. The opioid receptor in the migraine brain appears to work differently, leading to both ineffective pain relief and medication overuse headache (MOH)[9] – a secondary condition caused from using normal pain relief more than 10 days per month – so we need pain relief that is not going to make our health worse. The way serotonin is processed appears to be different in people with migraine, with most migraine patients doing badly on SSRIs and SNRIs[10]. Again, much more primary research is required to more fully understand the pathophysiology of migraine before effective treatments can be developed.

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[8] Faragó P, Tuka B, Tóth E, et al. Interictal brain activity differs in migraine with and without aura: resting state fMRI study. J Headache Pain. 2017;18(1):8. https://doi.org/10.1186/s10194-016-0716-8 ; Skorobogatykh, K., van Hoogstraten, W.S., Degan, D. et al. Functional connectivity studies in migraine: what have we learned?. J Headache Pain 20, 108 (2019). https://doi.org/10.1186/s10194-019-1047-3

[9] Jassar H, Nascimento TD, Kaciroti N, et al. Impact of chronic migraine attacks and their severity on the endogenous μ-opioid neurotransmission in the limbic system. Neuroimage Clin. 2019;23:101905. https://doi.org/10.1016/j.nicl.2019.101905

[10] Torta, R., Ieraci, V. Migraine and depression comorbidity: antidepressant options. Neurol Sci 33, 117–118 (2012). https://doi.org/10.1007/s10072-012-1055-4

Because the stumbling block for the migraine treatment market is at the primary research level, we believe (and have argued elsewhere before) that a National Health and Medical Research Council (NHMRC) targeted call for research, or perhaps a similar injection of research funds from the Medical Research Future Fund (MRFF), is the best thing that can be done to advance the understanding, management, and the development of new treatments for migraine in Australia. We also support the application (which has so far been rejected three times) for a centre of excellence into the epidemiology of migraine, as the greatest gains in treatment and management will undoubtedly come from a better understanding of what migraine is, who it affects, and the genetic and other characteristics of the disorder. As migraine treatment is a substantial global market with unmet demand, the return to those who are successful in developing new effective migraine treatments could be enormous.

3.3. Measures that could make Australia a more attractive location for clinical trials for new drugs and novel medical technologies

Migraine Australia cannot speak to what would make Australia more attractive for researchers and drug companies, but we can say that a fast-track process through the TGA and PBAC for drugs tested in Australia would encourage greater participation. As we have learned, one of the cruellest aspects of new medications coming to market is being able to trial them, have great success with them, and then have them taken away. For example, one of our members was on the clinical trial for Vyepti (a quarterly infusion version of the CGRP monoclonal antibody treatment) and achieved near curative success; she has not done as well on the competitor products. So, if a process could be developed whereby those having success on open label trials can continue with the therapy, that would be an excellent outcome for patients as well as well as a strong incentive for research to be done here.

Additionally, we believe that patient bodies, such as Migraine Australia, should be supported to provide recruitment and awareness assistance to those conducting the clinical trials. This will ensure that people are more aware of what trials are available and assist in educating the community on new treatments in the pipeline, thus enabling a smoother transition to new medications.

3.4. Without compromising the assessment of safety, quality, efficacy or cost-effectiveness, whether the approval process for new drugs and novel medical technologies, could be made more efficient, including through greater use of international approval processes, greater alignment of registration and reimbursement processes or post market assessment.

There is much we could say on this topic, but we will constrain ourselves to positive suggestions that may help others avoid the significant frustrations we are still enduring. Absolutely, safety, quality, efficacy and cost effectiveness should never be compromised, but the process could be considerably more efficient. The TGA process appears to work well and have a high level of transparency and trust. Yes, it could be faster, and perhaps work in closer collaboration with its US (FDA) and European (EMA) counterparts, but we do not want to completely outsource safety controls to foreign agencies as we cannot control or know if they are ever compromised. The only minor suggestion we have for TGA processes is that there seems to be a very low rate of reporting of side effects and adverse events to the TGA, and perhaps that reporting process could be made simpler and more consumer friendly.

In stark contrast to the TGA process, the reimbursement processes are simply woeful. We understand this may be nobody's fault but rather is the inevitable result of a process that has been developed in an ad hoc fashion over many years. The following are our suggestions, and we are more than happy to work with the Department or others on developing these ideas further.

3.4.1. Overhaul the PBAC process to remove planned failure

The current PBAC process is designed to expect resubmission: it is designed for new medications and/or technologies to fail. Aside from being a hideously expensive and cumbersome exercise, it delays the delivery of new medications to Australians. The entire system needs to be overhauled to remove that planned failure. A system where any issues are worked out with Department of Health staff in advance of the PBAC decision process, so that the proposal that arrives on the PBAC agenda is ready for their decision without any unanswered questions, would be a healthier, more efficient, and a far less traumatic experience for patients.

The 17-week cycle also limits resubmissions so that any rejections or deferrals necessitate many months in delay. Recent changes to the categories and re-submission process seem to be further entrenching that planned failure rather than eradicating it. Combined with the massive fees for a major submission, the entire process appears to be designed to frustrate drug companies and extract money out of them while protecting the health budget from increased spending. The PBAC approval system, like the entire health system, should be working for patients, not the Government or drug companies. The PBAC process (or a replacement process) ought to realign its focus on the health and wellbeing of Australians.

3.4.2. Have early and transparent stakeholder consultations with patient and doctor bodies

From a patient perspective, it is difficult to engage with a PBAC process when there is insufficient information provided from PBAC. Our recent lengthy submission to the PBAC about Emgality detailed our issues with the restrictions identified from *prior* Public Summary Documents (PSDs), however, we don't actually know if those issues are in the current application. What price is negotiated is not something we can really comment on nor affect; however, which patients qualify, who can prescribe, and other very real restrictions that affect people's ability to get the treatment that they need is something we care about very deeply. Not being informed of those restrictions are until after the decision has already been made prevents us from being able to inform either the drug company or the PBAC if they are logical and workable, or are – as we have seen with our CGRP drugs – completely inappropriate and demonstrative of a failure to understand our condition and how migraine is managed.

Bringing doctor and patient bodies in for consultations before a submission is made to PBAC, or very early in the PBAC process, should be required. Where an appropriate patient or doctor body does not exist, targeted research should be conducted to determine the acceptability of the proposed restrictions. This consultation or research could be conducted while the company is waiting for TGA approval of the medication, thus ensuring that there is no additional delay to listing. It would also give PBAC greater confidence that there will be less use of the medication outside of the restrictions if those restrictions have been designed in consultation with the people who are directly affected by them.

As a very basic step, allowing people to see the application they are submitting comments upon is essential for transparency and will make the process more efficient and effective. By all means, censor the dollar figures as they do in the PSDs, but we cannot make useful informed comment without seeing what we are commenting on.

3.4.3. Enable patient or doctor bodies to initiate stakeholder meetings and appeal decisions of the PBAC

The current process for convening a stakeholder meeting in the event that PBAC finds itself unable to recommend a drug on the basis of cost-effectiveness only permits either PBAC, or the sponsor, to request the meeting. Such meetings are not an appeal process – there is currently no appeal process – but they are an ability for stakeholders to be heard. Migraine Australia has observed that, in practice, drug companies are very reluctant to use the review or stakeholder processes for fear of repercussions from the PBAC. Thus, those who are directly affected – the doctors and patients – must be provided the ability to call for a stakeholder meeting. Further, an appeal process which again can be used by doctor and patient bodies, not just the sponsor, should be introduced to the system. From our own experience, not being able to appeal or have any input into the Aimovig rejection is frustrating, heart breaking, and demonstrates just how powerless patients and doctors are in this process.

3.4.4. Drop the requirement for a comparator for first-in-class medications

The current process of requiring new drugs to have a comparator should be scrapped when there is no real comparator drug. The vast majority of issues there have been with getting the CGRPs listed, from the risk sharing agreement to the restrictions on which patients qualify, can all be linked back to the Botox comparator. Botox for migraine treats head pain by inhibiting acetylcholine and blocking action on the parasympathetic nervous system[11], thus breaking the pain feedback cycle of persistent headache rather than treating or managing the underlying migraine itself. Botox has never been approved as safe or appropriate for use for

[11] Binder WJ, Brin MF, Blitzer A, Pogoda JM. Botulinum toxin type A (BOTOX) for treatment of migraine. Semin Cutan Med Surg. 2001 Jun;20(2):93-100. doi: 10.1053/sder.2001.24423. PMID: 11474749.

anything except Chronic Migraine (15 or more headache days per month). We are not sure where and how these new migraine treatments started being measured against Botox, but they never should have been – the new medications are migraine treatments, not head pain treatments.

This practice of requiring a comparator for first-in-class medications we feel is the most distorting feature of the entire registration/reimbursement system for pharmaceuticals. The clinical trials are, as a result, designed to test against the comparator, rather than test the drug for what the scientists believe it does. All of the material about the new drug uses the language of the inappropriate comparator, and everything the drug companies do in bringing that new product to market is designed to achieve reimbursement. So, in the example of CGRPs, developed as a result of innovative science and the first medications designed to prevent migraine attack – not simply treat symptoms of migraine – we have multiple companies who have designed all their clinical trials, and developed rafts of materials, seeking a reduction in headache days for Chronic Migraine patients using the same efficacy endpoints as Botox. The FDA now requires migraine treatments efficacy endpoints to be measured by reduction in 'most bothersome symptom', better accounting for the complexity and variability of migraine[12]; it does not appear that the TGA nor PBAC use this better measure of reduction in 'most bothersome symptom'.

The CGRP medications are far more successful in clinical practice than they were in the trials as a result, working well for patients with low or minimal headache but high levels of disability from migraine. But while the medical science community is having a conversation about reduction in migraine disability, the reimbursement (PBAC) process is discussing headache. They're debating restrictions that require us to trial outdated, ineffective and off label medications before we can have these new drugs of much higher efficacy, and restrictions for a reduction of headache days to continue treatment. We're fighting very, very hard to change the restrictions and language so there are better comparators for many other new drugs in development, but we shouldn't have to fight this hard. And we shouldn't

[12] FDA, Migraine: Developing Drugs for Acute Treatment; Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER); February 2018, https://www.fda.gov/media/89829/download

require pharmaceutical companies to compromise their products to fit a bureaucratic check box: first in class means there is no comparator.

3.4.5. Require a whole of budget impact analysis for new drugs without comparator

Having Aimovig rejected, and Emgality and Ajovy so far not listed because of the impact on the health budget is an extremely difficult thing for our community to deal with. The hardest part is that we believe that, in a holistic assessment of the benefits of the medication, not listing these medications is ultimately costing taxpayers more money in health care and welfare, as well as lost productivity. As young people with families and entire careers sacrificed to this disease, we know that facilitating access to such medications will in many cases enable us to get off welfare and go back to work. We estimate that if just a third of those on disability support pension (DSP) because of migraine were able to get off DSP and return to a full and contributing life, the savings to the welfare budget along would cover the entire annual cost of these medications.

That does not include increased tax revenue, or decreased burden on Medicare and hospitals, or on disability support and other care services, or family members being able to work more because they're not having to take care of us, or even the improvement in the gender pay gap by keeping up to a quarter of women aged 25-45 at work and moving up the hierarchy, or any of the other flow on benefits. Migraine Australia believes that were a holistic cost-benefit analysis of the outcomes from CGRP use to be undertaken, the benefits would far outweigh the cost of the medication in the health budget (which is all that PBAC is concerned with).

When it is a drug for an unmet need, particularly first-in-class medications, the Department of Finance (or Treasury or another body as is deemed appropriate) should be asked to provide a whole of budget impact analysis. Without that whole of budget view, every new drug for an unmet need will be judged an increased burden on the health budget and thus, by PBAC's standards, rejected. This is a massive disincentive for pharmaceutical companies to bother developing new drugs at all. There must be a mechanism to look at the broader financial (and potentially other) implications, and if the additional expenditure in the PBS budget will be offset elsewhere, then this should be taken into account. The Parliamentary

Budget Office contains significant modelling expertise and could easily undertake this analysis, but they must be tasked with doing this, as it is not within their remit to do exploratory analysis. Drug companies should be incentivised to develop products that improve the whole nation through decreased disability and increased productivity, to maintain or improve quality of life, not simply to keep someone alive for a bit longer.

3.4.6. Have a real-world trial built into the new drug assessment process

As mentioned in our story detailed in part 1 of this submission, the limitation of patient familiarisation programs to 10 patients per doctor created some very unfair situations where one patient gets treatment while another, equally deserving patient, with the same condition and the same doctor, does not. The other issue that has repeatedly hampered the listing of the CGRP medications is there is no understanding of potential patient numbers for treatment. Including a real-world trial into the PBAC assessment process, enabling any patient who fits the criteria to take part, would give PBAC very solid data on which to do their analysis and assessments, while at the same time ensuring that patients are not denied access to potentially life changing medications while they deliberate.

3.4.7. Re-implement a separate process to negotiate on pricing

It may seem counter-productive to want to re-implement the Pharmaceutical Benefits Pricing Authority when it was only abolished 6 years ago, but from our perspective, having PBAC making decisions about whether a drug should be recommended for listing on non-clinical factors such as price or budget impact undermines the integrity and credibility of the process. PBAC should, as a body comprised mostly of doctors, only be considering the safety, efficacy, and comparable benefits of any given medication. As we have seen with the CGRPs, even though every application the PBAC has found these drugs to be safe, effective, and cost effective, there are questions raised about safety and efficacy because there is no agreement to list. This is a reality driven entirely by the risk share agreement proposed and the surrounding debate. These questions are not idle gossip: the Health Minister himself raised questions about the safety and efficacy of Emgality in the House chamber. There are no concerns about safety or efficacy of Aimovig, Emgality or Ajovy, and Migraine Australia are performing damage control, reassuring people their medications are safe. It is extremely

important that patients' trust in their medicines is not undermined by haggling over price, and thus these two parts of the process should be handled separately.

3.4.8. End the use of 'risk share agreements' to artificially limit PBS expenditure

As we understand it, risk share agreements were intended to limit the Government's exposure if the medications are prescribed for something outside of the indication. While this is a fair and reasonable thing, the risk share agreements have morphed into a tool that is not about sharing risk, but about limiting PBS expenditure. The proposal to include Ajovy and Emgality under the existing Botox cap would require Teva and Lilly respectively to fund 9 out of 10 patients, with the Government only paying the heavily discounted 'special buy' price for 1 patient in 10. This is not a commercially viable requirement and is particularly punitive on those disorders that affect large numbers of people. Every citizen has a right to access PBS subsidised medications for their condition; we should not be forced to hope for the philanthropy of drug companies because we have a widespread disorder.

3.4.9. Automatically list alternative preparations and pack sizes

The need to go back to PBAC with another submission to add different preparations and pack sizes would seem to be highly inefficient and a waste of the PBAC's time. If it is the same medication, just in a dissolvable wafer or nasal spray rather than a tablet, or a pack of 30 instead of a pack of 10, that formulation has been TGA approved as safe and it is used by the same cohort of patients for the same purpose, and sold for a comparable price, then companies should be able to just register the different formulation or pack size with the Department. It is really quite puzzling to us why Palexia (an analgesic) standard release is on the PBS but immediate release formulation is not, or why Imigran (a triptan for the acute treatment of migraine) in a tablet is on the PBS, but the injections are not, and so on.

3.4.10. Enable a quick and affordable process for older drugs currently only on the PBS to have their restrictions altered through a departmental process when requested by third parties such as patient bodies

Following on from point 2.4.9 above, the array of medications that are on the PBS for another condition but not for migraine is perplexing, especially when those medications are

generic and the cost to the PBS is minimal. For example, Ondansetron, a very effective antiemetic wafer used by many in the migraine community, is only on the PBS for cancer patients. And, while a private script is only around $15-$18 on average, for those who are on benefits and are entitled to the lower co-pay of $6.60, that $8-$11 per script matters. Or, for another example, 100mg tablets of topiramate (an anti-convulsant commonly used to attempt to reduce migraine attacks) are listed on the PBS for epilepsy but not for migraine. However, the 50mg tablets are listed on the PBS for migraine. It costs both the patient and the Government more for those who are on 100mg of topiramate twice a day for migraine to provide two boxes a month of the 50mg rather than one box of the 100mg. It doesn't make any logical sense. These anomalies may not be possible to ascertain at the time of initial listing: there should be a simple mechanism to sort these things out effectively and without putting additional burden on the listing process. This alteration mechanism must be affordable: patient bodies do not have the more than $40,000 for a minor submission, or $15,000 just to get a meeting.

3.4.11. Change the composition of the PBAC often

We are particularly concerned by the level of arrogance displayed by certain members of the PBAC: a general attitude of being accountable to no one, that they can do what they like, or that they hold all the cards, we feel is not appropriate for a public service body of this kind. We believe there is entrenched bias within the committee, possibly linked to the expertise on the committee (an over-representation of expertise on medical conditions primarily affecting older members of the community, such as cancer and arthritis, plus a gerontologist, for example, may account for the apparent bias against diseases that predominantly affect the young). We believe that the current committee is compromised in its independence. There is some evidence to suggest that the committee is subservient to the Health Minister in artificially limiting PBS expenditure.

We believe the committee could significantly benefit from a more frequent refresh of its members. Under the legislation, members are appointed by the minister and serve at the minister's pleasure: if PBAC is truly an independent body that is not beholden to the minister, then appointments should be made by an independent process. The Minister should not be able to 'invite applications' from specific people, and professional and peak bodies should not

have the vetting power of making nominations. Set terms may also be of value; for example, two-year terms with a maximum of two terms. We would also suggest that the chair and deputy chair positions should only be held for a maximum of two years. Additionally, while seeking balance in all its forms, the preference should be more towards practicing clinicians over academics who may have little knowledge of the variables and realities of patient management.

3.4.12. Review the influence of pharmacists in post market dynamics

Pharmacists hold considerable sway over how drugs are actually dispensed and used. We feel that the role of pharmacists is often forgotten in the debate about medication access. As our vertical learning curve continues, and we are only just starting to get our heads around the equally opaque and confusing dealings between the government and pharmacists, and the other influences on pharmacists in how they assist patients. In addition to the 'dispensing fee' issue mentioned above, where pharmacists can charge anything they like to provide medications we should be getting for free under access programs, we have a number of concerns about triptans being downscheduled to be available over-the-counter from 1 February 2021. The move to downschedule triptans appears to be driven by the Pharmacy Guild solely for the purpose of increasing revenue. We were unaware this was even being discussed until it had happened – it certainly was not at the request of patients. We are not aware of any planning for appropriate awareness and education initiatives on how to use triptans effectively or safely, although we understand the Pharmacy Guild may have some pharmacist targeted efforts planned. While those who have a high level of migraine literacy will be advantaged by being able to access the medication they need when they need it, the risks for most people with poorly managed migraine are great. Additionally, there is considerable risk of people who are self-diagnosed being recommended given triptans by a pharmacist without any encouragement to talk to a doctor about their symptoms, which may lead to significant health issues (up to and including brain tumours) going undiagnosed. What medications are available, what people should ask their doctor about, and encouraging patients to try something new, are all very important roles of the local pharmacist. But there does seem to be some less-than-honest dealings at the distribution end of the system that need some oversight or critical review.

4. Conclusion

The existence of Migraine Australia is inextricably linked with the issues in bringing new drugs to the Australian market. Our experience of needing to organise to try and lobby for access to medications that are life-changing and cost effective goes against the grain of what most Australians believe about our PBS. We feel the TGA process works well, but the PBAC process is inadequate and compromised, and needs significant reform. We have made a number of suggestions to remove or limit bias in the PBAC, further involve consumers in the process, and end the distorting influence of the reimbursement and access systems on the way new drugs are brought to market.

There are some very serious issues we have raised here about the PBS/PBAC process and the role of pharmacists. While this inquiry into new drugs is very welcome, we feel the Standing Committee should give some thought into whether a bigger and broader inquiry (possibly even a royal commission) into the entire pharmaceutical system in this country is warranted. We do not use words like unfair, bias, compromised, or risk lightly: we use these words as an accurate indicator of what we have observed. The PBS system in its entirety may require a significant overhaul, including potentially starting from scratch to design a better reimbursement process, and possibly reform at the distribution end with pharmacists.

Migraine Australia and all the people we represent are angry, disillusioned and suffering, but we welcome any and all efforts to improve the process of bringing new medications, particularly those for unmet needs like managing migraine, to Australians. Thank you again for this opportunity. We are happy to answer any questions the Committee may have and attend a hearing to give further evidence.