Record of the Neurological Advisory Committee Meeting held on 19 September 2023

Neurological Advisory Committee records are published in accordance with the Terms of Reference for the Specialist Advisory Committees 2021.

Note that this document is not necessarily a complete record of the Neurological Advisory Committee meeting; only the relevant portions of the meeting record relating to Neurological Advisory Committee discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

The Neurological Advisory Committee may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or Specialist Advisory Committees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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1. Attendance

Present
Brian Anderson (Chair)
Christine Pihema
John Fink (Zoom)
John Mottershead
Lynette Sadleir
Paul Timmings
Sarah Buchanan

Apologies
Giles Newton-Howes

Other attendees
Dr Fiona Imlach (Migraine Foundation Aotearoa)
Suzanne Vale (Migraine Foundation Aotearoa)
Dr Desiree Fernandez (Migraine Foundation Aotearoa)

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Rotigotine for the treatment of Parkinson's disease	High Priority
• Subcutaneous Natalizumab for the treatment of relapsing remitting multiple sclerosis	Medium Priority
• Lacosamide oral liquid for the treatment of focal epilepsy	High Priority
• Erenumab, galcanezumab, and atogepant for chronic migraine	High Priority
• Erenumab, galcanezumab, and atogepant for episodic migraine	High Priority

- Siponimod for the treatment of active secondary progressive multiple sclerosis — Medium Priority

3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Neurological Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) 2021 and Specialist Advisory Committees 2021 Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 6.4 of the SAC Terms of Reference.

3.3. The Neurological Advisory Committee is a Specialist Advisory Committee of Pharmac. The Neurological Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Neurological Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for neurological treatments that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for neurological treatments that differ from the Neurological Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac considers the recommendations provided by both the Neurological Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for neurological treatments.

4. Welcome and introduction

4.1. The Chair opened the meeting with a karakia (prayer) and mihimihi (acknowledgements). Then there was a round of whanaungatanga (introductions and relationship building). The Chair welcomed the Committee.

5. Record of Neurological Advisory Committee meeting held Friday, October 29, 2021

5.1. The Advisory Committee reviewed and accepted the record of the Neurological Advisory Committee meeting held on Friday 29 October 2021.

6. Correspondence and Matters Arising

Levodopa, carbidopa, entacapone

Discussion

Māori impact

6.1. The Committee noted that Parkinson's disease is not considered to be a part of Pharmac's Hauora Arotahi (Māori health areas of focus). The Committee noted a New Zealand study that identified a low incidence of Parkinson's disease in Māori; the 2006-2013 age-standardised incidence per 100,000 population per year was New

Zealand European, 33; Asian, 28; Pasifika, 27; Māori 20 (Pitcher et al. Mov Disord. 2018;33:1140-8).

6.2. The Committee considered that although the prevalence of Parkinson's disease in Māori is likely to be less than in non-Māori, the impact of diagnosis on health outcomes would likely be greater in Māori. The Committee considered that Māori are likely to experience delayed diagnosis and increased barriers to accessing primary health care, neurology services, pharmacies, and community nurses. The Committee noted that although disease predominantly affects older populations, Māori older adults may be at more risk of medicines-related harm than younger and non-Māori populations (Hikaka et al. Drugs Aging. 2021;38:205-17).

Background

6.3. The Committee noted that Pharmac currently funds levodopa 100 mg with carbidopa 25 mg tablet (Sinemet), levodopa 250 mg with carbidopa 25 mg tablet (Sinemet), levodopa 200 mg with carbidopa 50 mg long-acting tablet (Sinemet CR), and entacapone 200 mg tablet (Comtan). The Committee noted that the levodopa 100 mg with carbidopa 25 mg tablet currently has the highest usage of these formulations.

6.4. The Committee noted that there have been various brands of levodopa/carbidopa tablets funded over time, due to entrenched supply issues associated with previous tender outcomes. The Committee noted that for most people, previous brand changes have not been an issue, however there were some people who expressed a preference for one brand over another.

Levodopa/carbidopa/entacapone combination tablet

6.5. The Committee noted that a combination tablet containing levodopa/carbidopa/entacapone (Stalevo) is widely available internationally and is used in the United Kingdom and Australia. The Committee noted that there are several pharmaceutical companies interested in supplying this combination tablet to the New Zealand market. The Committee noted that, due to this interest, this product has been included in the proposed 2023/24 Invitation to Tender. The Committee noted that suppliers of levodopa/carbidopa/entacapone tablets would need to gain Medsafe approval before commencing supply through a tender award.

6.6. The Committee noted that the levodopa/carbidopa/entacapone tablet is available in a variety of strengths (listed below). The Committee considered that levodopa/carbidopa/entacapone 50/12.5/200 mg, 100/25/200 mg, 150/50/200 mg, and 200/50/200 mg would be the strengths most likely to be used for people with Parkinson's Disease.

- Tab 50 mg with carbidopa 12.5 mg and entacapone 200 mg
- Tab 75 mg with carbidopa 18.75 mg and entacapone 200 mg
- Tab 100 mg with carbidopa 25 mg and entacapone 200 mg
- Tab 125 mg with carbidopa 31.25 mg and entacapone 200 mg
- Tab 150 mg with carbidopa 37.5 mg and entacapone 200 mg
- Tab 200 mg with carbidopa 50 mg and entacapone 200 mg

6.7. The Committee noted that the levodopa/carbidopa/entacapone tablet is used more readily overseas, and therefore considered that funding this agent would better align New Zealand with other countries. The Committee considered that this would also reduce the risk of future supply issues, which as described previously have been an ongoing issue for levodopa/carbidopa immediate release and controlled release tablets and creates anxiety for people taking these medicines. The Committee also

noted that the availability of new levodopa/carbidopa products or different strengths has the potential to create complexities and confusion amongst healthcare professionals and people taking these medicines.

6.8. The Committee noted one publication that reported on a series of pharmacokinetic studies demonstrating bioequivalence between the Stalevo brand and corresponding dosages of levodopa/carbidopa immediate release tablets taken with entacapone tablets (Hauser R. Neurology. 2004;13;62). The Committee noted that this study reported clinical advantages of Stalevo in enabling people to take one tablet rather than two (or more) separate tablets, and that levodopa/carbidopa/entacapone 50/12.5/200 mg (Stalevo 50) and 100/25/200 mg (Stalevo 100) tablets are smaller than entacapone tablets. The Committee noted that that study results showed that most people taking levodopa/carbidopa immediate release tablets with entacapone tablets can be directly switched to the corresponding dose of the Stalevo product.

6.8.1. The Committee noted that for those with fluctuating Parkinson's disease who take levodopa/carbidopa immediate release tablets without entacapone, switching to the corresponding Stalevo tablet is analogous to adding entacapone.

6.8.2. The Committee considered that in those switching between formulations who are receiving levodopa/carbidopa-controlled release, prescribers would need to be aware that the bioavailability of levodopa from levodopa/carbidopa controlled release is approximately 70-75% that of levodopa/carbidopa immediate release products, including Stalevo.

6.9. The Committee considered that levodopa/carbidopa/entacapone combination tablets would provide various suitability advantages as noted in the Hauser publication, including the ability to reduce the number of tablets taken by an individual and reduced size of tablets.

6.10. The Committee considered that levodopa/carbidopa/entacapone combination tablets provide a similar health benefit to the levodopa/carbidopa immediate release tablets taken together with entacapone tablets. Members considered that the fixed dose of entacapone 200 mg in the Stalevo combination tablets would align with how entacapone is often prescribed, although there may be some circumstances where a fixed dose of entacapone is less suitable as it would not allow for dose adjustments to manage side effects such as dyskinesia.

6.11. The Committee considered that people newly diagnosed with Parkinson's Disease would likely be prescribed levodopa/carbidopa, and that entacapone may be added as an additional treatment at a later stage based on the person's response to treatment. The Committee therefore considered that the levodopa/carbidopa/entacapone combination tablet would be prescribed to those already initiated on levodopa/carbidopa and requiring entacapone, or people already taking levodopa/carbidopa tablets plus entacapone 200 mg tablets.

Possible brand changes for levodopa/carbidopa tablets

6.12. The Committee noted that it previously considered the implications of a brand change for levodopa/carbidopa tablets at its 2016 meeting. The Committee (then Subcommittee) noted that people with Parkinson's disease have a high health need, and therefore sufficient support from Pharmac and the health sector would be required to implement a brand change for levodopa/carbidopa tablets.

6.13. The Committee considered that if the levodopa/carbidopa/entacapone presentations were to be funded, the variety of strengths and combinations of treatments could create confusion amongst people taking these medicines and their healthcare

professionals. The Committee therefore considered that clear messaging would be necessary to communicate the differences between available presentations.

6.14. The Committee considered that the type of healthcare professional who would manage a brand change for levodopa/carbidopa would depend on which formulations an individual was changing between.

6.14.1. The Committee considered that if an individual were to transition from taking levodopa/carbidopa tablets to a levodopa/carbidopa/entacapone combination tablet (ie this was their first time taking entacapone), this would be managed by a neurologist.

6.14.2. The Committee considered that if an individual were to transition from taking levodopa/carbidopa tablets plus entacapone tablets to a levodopa/carbidopa/entacapone combination tablet, this could be managed by the person's general practitioner.

6.15. It was considered however that some general practitioners may not be comfortable making this change without the guidance of a neurologist. The Committee therefore considered that the uptake of levodopa/carbidopa/entacapone would likely be slow. The Committee considered that pharmacists could be involved in educating people who may be prescribed the levodopa/carbidopa/entacapone product.

6.16. The Committee considered that there would not need to be any particular monitoring requirements for an individual transitioning from levodopa/carbidopa immediate release tablets plus entacapone tablets to the levodopa/carbidopa/entacapone combination tablet, however considered that regular monitoring of the person's symptoms would be necessary.

7. Rotigotine for Parkinson's disease

Application

7.1. The Committee reviewed the September 2022 clinician application for rotigotine patches (Neupro) for the treatment of Parkinson's disease. The Committee noted that this application was considered by PTAC in February 2023.

7.1.1. The Committee noted that Pharmac staff had also received correspondence from The Parkinson's New Zealand Charitable Trust and several neurologists regarding this funding application.

7.2. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

7.3. The Committee **recommended** that rotigotine be listed with a **high priority** within the context of neurology treatments, subject to the following Special Authority criteria:

> ROTIGOTINE – Parkinson's disease
> Applications from any relevant practitioner. Approvals valid without further renewal unless notified where the treatment remains appropriate and the patient is benefiting from treatment.
> 1. Person has advanced Parkinson's disease requiring treatment with a dopamine agonist; and
> 2. Either:
>
> 1.1. Person is unable to take oral medications acutely or otherwise (eg due to severe dysphagia, or being nil by mouth due to acute illness or medical procedures); or
> 1.2. Person would benefit from a treatment with a longer therapeutic half-life, such as those who experience severe, problematic or disabling Parkinson's symptoms (eg sleep disturbance/nocturnal symptoms, a high risk of impulse control disorder, difficult off-time).

7.4. In making this recommendation, the Committee considered:

7.4.1. The significant health need of people with Parkinson's disease (PD) and its impact on carers especially where there are severe, problematic, and disabling PD symptoms, such as impulse control disorders (ICD);

7.4.2. That ICD affect 20-40% of people with PD who receive treatment with non-ergot dopamine agonists;

7.4.3. That rotigotine would have a beneficial therapeutic effect in reducing the risk of ICD in this context and its longer therapeutic half-life (compared with currently funded non-ergot dopamine agonists) would lead to more effective management of problematic and disabling PD symptoms.

Discussion

7.5. PTAC and PTAC Advisory Committees may differ in the advice they provide to Pharmac, including recommendations priority, due to the Committees' different, albeit complementary, roles, expertise, experience, and perspectives.

Māori impact

7.6. The Committee noted that PD is not considered to be a part of Pharmac's Hauora Arotahi (Māori health areas of focus) and that Māori experience different health outcomes when compared with non-Māori. The Committee noted the paucity of evidence for Māori in PD and considered it would have been useful to understand usage of Parkinson's medicines specifically in ethnic groups detailed by age, and whether there is any preference among Māori for an oral medicine or patch for use in PD.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system

7.7. The Committee noted the possible impact of funding rotigotine for the treatment of PD disease on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee was not aware of any groups experiencing health inequities disproportionately affected by PD or its treatments.

Background

7.8. The Committee noted that a supplier application for rotigotine patches was previously considered by PTAC in 2014, which recommended the product be listed as cost-neutral to other non-ergot dopamine agonists (pramipexole or ropinirole). The Committee noted that the application was formally declined in March 2022 by Pharmac (before the current application was received) as cost-neutrality was unable to be reached.

7.9. The Committee noted that the current funding application was received in September 2022 and reviewed by PTAC in February 2023. The Committee noted that, at that time, PTAC recommended rotigotine patches for PD be listed as cost-neutral to other funded non-ergot dopamine agonists (pramipexole or ropinirole). The Committee noted that in making this recommendation that PTAC had considered:

- Rotigotine patches are non-inferior to other dopamine agonists currently funded (pramipexole or ropinirole), and funding of this proposal would provide an additional option for non-ergot dopamine agonist treatment in PD with an alternative formulation
- Rotigotine patches had been associated with decreased risks of ICDs, [which PTAC considered to be] a rare adverse event. Due to [what PTAC considered to be] the rarity of this event, the potential magnitude of this benefit was not sufficient [according to PTAC] to suggest a significant benefit over other currently

funded non-ergot dopamine agonists. Additionally, rotigotine patches are associated with [what PTAC considered to be] a greater risk of adverse events overall compared to other non-ergot dopamine agonists.

- Within the non-ergot dopamine agonists class, there are two currently funded alternatives (pramipexole and ropinirole), and there are other funded alternatives for treatment of PD in other classes.

7.10. PTAC had recommended Pharmac staff seek further advice from the Neurological Advisory Committee regarding whether there are subgroups of individuals with higher health need than the general PD population, or who would benefit from rotigotine patches, such as, but not limited to, people who are unable to take oral medications acutely or otherwise; with morning off-time; with sleep disturbance; with dementia, or with other non-motor symptoms.

Health need

7.11. The Committee considered that people with PD have a significant health need and that there is a substantial impact on carers as a result of personal care issues, nocturnal issues, the impact on family sleep, and in some cases harm to family from ICD. The Committee considered that some people with PD have a need for a treatment with a longer therapeutic half-life due to, for example, difficult nocturnal symptoms, major concerns about ICD, or an inability to take oral treatments. The Committee considered that this represents an unmet need for those requiring effective management in certain circumstances rather than an unmet need in specific groups with specific PD-related symptoms. The Committee considered that those who have a high health need for more effective management could be described as follows:

- *people with advanced PD requiring treatment with a dopamine agonist who are unable to take oral medications acutely or otherwise (eg due to severe dysphagia, or being nil by mouth due to acute illness or medical procedures) and/or who would benefit from a treatment with a longer therapeutic half-life, such as those who experience severe, problematic, or disabling Parkinson's symptoms (eg sleep disturbance/nocturnal symptoms, a high risk of impulse control disorder (ICD), difficult off-time).*

7.12. The Committee noted that the PD treatment paradigm is variable and that a range of medicines may be used in different sequences, with some agents used earlier by some clinicians (eg dopamine agonist used early to delay initiation of levodopa) and used later by others, or not used at all. The Committee noted that a similar variable paradigm is seen in Australia resulting from prescriber preference.

7.13. The Committee considered that access to an agent with a longer therapeutic half-life would provide more effective management of problematic and disabling PD symptoms.

7.14. The Committee noted the paucity of evidence for Māori with PD and considered it would have been useful to understand usage of Parkinson's medicines according to ethnicity and age group.

Health benefit

7.15. The Committee discussed PTAC's February 2023 noting of rotigotine patches' association with reduced ICD, where PTAC had considered ICD, as an adverse effect from other currently funded non-ergot dopamine agonists, to be rare in its view. The Committee noted that PTAC had therefore concluded that rotigotine consequently provided insufficient incremental benefit over those agents.

7.16. The Committee was unable to agree with PTAC's views. Instead, the Committee considered:

7.16.1. ICD as an adverse effect from dopamine agonists is relatively common. The Committee noted that ICD in PD arises from treatment with dopamine agonists and there is evidence that ICD occurs in 20-40% of adults with PD treated with dopamine agonists (Rizos et al. Eur J Neurol. 2016;23:1255-61; Garcia-Ruiz et al. J Neurol Neurosurg Psychiatry. 2014;85:840-4). The Committee also noted evidence cited in the application reported a substantially reduced incidence of ICD with rotigotine (4.9%) vs pramipexole immediate release (19%) (Rizos et al. 2016) and considered that there were other studies reporting similar results (Garcia-Ruiz et al. 2014).

7.16.2. Rotigotine patches should be available in addition to the two funded alternatives (pramipexole and ropinirole), rather than being cost neutral to them; with the comparator being apomorphine (not pramipexole or ropinirole).

7.17. The Committee noted that rotigotine has an enduring therapeutic effect lasting 24 hours, which the Committee considered would be highly beneficial for those with severe/disabling nocturnal PD symptoms by ensuring therapeutic dopamine concentrations are maintained overnight.

7.18. The Committee considered that there were some potential concerns with rotigotine (eg dosing risks from using too many patches at once, and also the risk of skin reactions) and acknowledged that rotigotine patches are non-inferior to the other non-ergot dopamine agonists currently funded (pramipexole or ropinirole) in terms of Unified Parkinson's Disease Rating Scale (UPDRS)-assessed parkinsonism. The Committee considered that there may be a class effect with non-ergot dopamine agonists for the treatment of PD, however that there was evidence patches provide a more consistent rate of delivery compared with oral controlled release formulations in this setting, and this would be relevant in the context of PD with problematic and disabling symptoms.

7.19. The Committee noted that the quality of evidence for the use of rotigotine in PD was variable, however that there was moderate quality evidence for its use in:

- people unable to take oral medications acutely or otherwise (Frampton. CNS Drugs. 2019;33:707-18 ; Lenka et al. Can J Neurol Sci. 2021;48:299-307; Hirano et al. Dysphagia. 2015;30:452-6; Raeder et al. CNS Drugs. 2021;35:215-31).
- people with morning off-time and sleep disturbance/nocturnal symptoms (Trenkwalder et al. Mov Discord. 2011;26:90-9; Ghys et al. Expert Opin Pharmacother. 2011;12:1985-98; Pierantozzi et al. Sleep Med. 2016;21:140-4; Bhidayasiri et al. Parkinsonism Relat Disord. 2017;44:124-8).

7.20. The Committee noted evidence for rotigotine for the treatment of PD in people with other non-motor symptoms (eg swallowing difficulties) (Chaudhuri et al. Parkinsonism Relat Disord. 2013;19:660-5; Antonini et al. Eur J Neurol. 2015;22:1400-7; Hauser et al. BMC Neurol. 2016;16:90; Kassubek et al. BMC Neurol. 2014;14:42; Chung et al. Expert Opin Pharmacother. 2016;17:1453-61). The Committee considered that while these symptoms were relevant to quality of life, it was uncertain from the evidence whether there is a benefit in this setting. The Committee therefore considered it reasonable not to specifically mention these symptoms in the funding criteria.

7.21. The Committee noted the lack of evidence for rotigotine use among people with dementia and Members considered that it would not be used in this context if symptoms could be managed with other agents, except in end-stage palliative care.

7.22. The Committee noted evidence discussing medicine administration in people with PD with a high pill burden which recommended education and support rather than a

switch from an oral to transdermal formulation (Oad et al. Dysphagia. 2019;34:119-28)

7.23. The Committee considered the key benefits of rotigotine were the reduction in risk of ICD and improved management of severe/disabling PD symptoms including nocturnal problems. The Committee considered that rotigotine patches would be very useful to fund and would make a difference to individuals with PD and their carers/families currently struggling with problematic and disabling impacts of PD.

Suitability

7.24. The Committee considered that rotigotine would be advantageous as a transdermal patch rather than another oral formulation, noting both pramipexole and ropinirole are oral tablets.

7.25. The Committee considered it was unknown, due to a lack of information, whether there is any preference for an oral medicine or patch for use in PD among Māori, Pacific peoples, disabled people, tāngata whaikaha Māori, or people who have been underserved by the health system.

Cost and savings

7.26. The Committee considered that if rotigotine were to be funded, it would sit alongside the other funded non-ergot dopamine agonists pramipexole and ropinirole in the treatment paradigm for PD. The Committee considered that the majority of people who would receive rotigotine would be requiring treatment with a non-ergot dopamine agonist but were experiencing, or are at high risk of developing, ICD with other funded non-ergot dopamine agonists. The Committee considered there may also be a large group of people eligible for rotigotine who are experiencing difficult nocturnal symptoms.

7.27. The Committee considered that rotigotine may replace 25% to 30% of the use of other dopamine agonists. The Committee considered that there may be a small group of people who cannot use other funded non-ergot dopamine agonists for a range of other reasons, but could use rotigotine.

7.28. The Committee considered that the subpopulation with PD who are unable to take oral medications acutely (or otherwise) would be small.

7.29. The Committee considered that rotigotine would not replace the use of apomorphine infusions. The Committee noted that apomorphine was typically reserved for the treatment of very advanced PD as it is a potent agent. The Committee considered that if rotigotine were funded, it may slightly delay the time before people require treatment with apomorphine as disease progressed.

7.30. The Committee considered that individuals who switched to rotigotine were unlikely to revert back to their previous medications unless they encountered adverse effects with rotigotine use.

Funding criteria

7.31. The Committee considered it appropriate to apply Special Authority criteria to rotigotine to target those most likely to benefit, with lifetime approval rather than requiring renewal, given that treatment with rotigotine would be ongoing until no longer required or it no longer provides benefit.

7.32. The Committee considered prescriber choice to be a strong factor when deciding which people would be prescribed rotigotine. The Committee considered that it would be more effective to target access according to the treatment needs of individuals who would benefit, rather than by specifying subgroups, and acknowledged overlap with subgroups suggested by PTAC. The Committee considered there were a

number of groups who could benefit from rotigotine, and making the access criteria for rotigotine too stringent would risk unintentionally excluding some groups.

Summary for assessment

7.33. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for rotigotine if it were to be funded in New Zealand for Parkinson's disease. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with Parkinson's disease, who would benefit from a dopamine agonist with a longer therapeutic half-life than other funded treatment options. This group includes people at high risk of developing, or who are currently experiencing, the following: • Sleep disturbance/nocturnal symptoms • High risk of impulse control disorder Difficult off-time	People with Parkinson's disease, who require treatment with dopamine agonists and are unable to take oral medications
Intervention	Rotigotine patches, assumed mean dosage of 6 mg per 24-hour period. Treatment duration is indefinite so long as rotigotine patches remain the most suitable treatment option.	
Comparator(s)	Other funded non-ergot dopamine agonists (pramipexole or ropinirole). Treatment duration is indefinite so long as pramipexole or ropinirole remain the most suitable treatment option.	
Outcome(s)	Compared to pramipexole or ropinirole, the main benefits of rotigotine are: • Longer therapeutic half-life o This may result in more effective management of problematic and disabling PD symptoms. • Decreased risk of impulse control disorders (ICD) o Rizos et al (Eur J Neurol. 2016;23:1255-61) reported that the rate of impulse control disorders was 4.9% with rotigotine patches compared with 19.0% for pramipexole immediate release formulations	
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.		

8. Natalizumab SC - relapsing remitting multiple sclerosis (RRMS)

Application

8.1. The Committee reviewed the application from Biogen NZ Biopharma Limited for the use of subcutaneous (SC) natalizumab (Tysabri) for the treatment of Relapsing Remitting Multiple Sclerosis (RRMS).

8.2. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

8.3. The Committee **recommended** that natalizumab SC be listed for the treatment of RRMS with a **medium priority**, within the context of neurology treatments, subject to the current multiple sclerosis (MS)-specific funding criteria.

8.4. In making this recommendation, the Committee considered that:

8.4.1. Natalizumab SC would provide a suitability benefit as an additional treatment option, especially for a subgroup of people with RRMS who have difficulty with intravenous (IV) access.

8.4.2. Natalizumab SC would require four-weekly (Q4W) administration due to risks associated with low trough drug levels when the SC formulation is administered by extended interval dosing. It would need to be administered in a clinical setting and accompanied by regular monitoring for John Cunningham Virus (JCV) and annual MRI scans.

8.4.3. As most of those currently on natalizumab IV are receiving six-weekly (Q6W) infusions, a switch to natalizumab SC Q4W would utilise more clinical resource than current treatment.

Discussion

Māori impact

8.5. The Committee discussed the impact of funding subcutaneous natalizumab for the treatment of RRMS on Pharmac's Hauora Arotahi (Māori health areas of focus) and Māori health outcomes.

8.6. The Committee noted that MS is not considered to be part of Pharmac's Hauora Arotahi (Māori health areas of focus) and that Māori experience different health outcomes when compared with non-Māori.

8.7. The Committee noted that there is a lower prevalence of MS in Māori compared with non-Māori and noted the paucity of data reporting on the severity of MS in Māori. However, the Committee considered that Māori experience greater barriers to access which may result in potentially worse MS health outcomes compared to non-Māori, and therefore considered that funding natalizumab SC may be advantageous to Māori with RRMS.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system

8.8. The Committee considered that funding natalizumab SC for RRMS may be advantageous for Pacific peoples with MS and people in underserved population groups with MS, as these groups may experience barriers to accessing infused treatments in a hospital or infusion centre setting.

Health need

8.9. The Committee noted that Pharmac currently funds eight pharmaceuticals for the treatment of MS, including natalizumab for IV infusion which has been funded since 2014 and is subject to the MS-specific funding criteria.

8.10. The Committee noted that natalizumab IV is recommended to be administered Q4W as described in the Medsafe data sheet, however, current practice internationally and for most people receiving this treatment in New Zealand is for Q6W dosing. The Committee noted that Q6W dosing saves infusion service time and resource, is effective for MS disease control, is associated with low incidence of anti-drug antibodies (ADA), and does not change the management of MS compared with Q4W dosing.

8.11. The Committee considered that there is robust New Zealand evidence that MS is less prevalent in Māori than in than Europeans and is also less prevalent in Pacific peoples than in NZ Europeans. However, the Committee noted that there is no data for the severity of MS in Māori and considered that barriers to healthcare access may result in later diagnosis in Māori and consequently, that Māori are likely to receive less benefit from treatment due to having higher EDSS score at the time of treatment commencement. The Committee also noted that Māori have higher rates of elevated BMI and smoking than European people, both of which are associated with worsening MS symptoms and disease progression (Manatū Hauora, Ministry of Health. 2021). The Committee acknowledged the substantial impact of MS on whānau in addition to the impact on the individual.

Health benefit

8.12. The Committee noted that the application proposed natalizumab SC for the treatment of people with RRMS with an EDSS score of 0-6, who meet the 2017 McDonald criteria and are receiving, or eligible to receive, currently funded RRMS treatments.

8.13. The Committee noted that natalizumab is a humanised monoclonal IgG4 antibody that acts to reduce central nervous system inflammation and demyelination by preventing lymphocyte migration across the blood-brain barrier. The Committee noted that when given IV, intra-individual natalizumab trough levels are often stable, but trough levels vary between patients. The Committee noted that natalizumab drug levels and consequent lymphocyte receptor saturation may be sensitive to dosing interval. The Committee noted that the supplier had provided estimates of lesser bioavailability with the SC formulation compared with the IV formulation, although elimination and half-life were similar based on provided data truncated at four weeks.

8.14. The Committee noted that the application proposed natalizumab SC be added into the treatment paradigm alongside other MS treatment options and that it would be expected to be used in place of natalizumab IV. The Committee noted that the application proposed Q4W dosing, however, that the evidence includes both Q4W and Q12W dosing regimens. Members noted that SC administration can be more immunogenically stimulating than IV and that this could lead to increased development of anti-drug antibodies (ADAbs).

8.15. The Committee noted that Medsafe registration for the natalizumab SC prefilled syringe (solution for injection) is currently undergoing QA review. The Committee noted that natalizumab SC has received mixed review outcomes from international regulators and funders, with recommendations from the European Medicines Agency (EMA) and in Australia (PBAC) and rejections by the US FDA and in Canada (CADTH).

8.16. The Committee noted evidence from REFINE (101MS206), an exploratory, dose- and frequency-blinded, prospective, randomised, dose-ranging phase 2 study investigating natalizumab IV and SC in six dosing regimens in 290 people with RRMS who were free of MS relapse for the 12 months prior to the study (Trojano et al. Mult Scler. 2021;27:2240-53). The Committee noted that all participants had received natalizumab prior to study enrolment, that there were small participant numbers per

arm for a clinical trial in the context of MS, and that the study was not powered to test equivalence or noninferiority of SC administration.

8.17. The Committee noted that all REFINE trial participants receiving natalizumab Q4W (IV or SC) received equally good outcomes, however, all those receiving Q12W (IV or SC) developed new lesions. The Committee noted that SC drug levels were continuously below the IV trough levels with 300 mg Q4W. The Committee noted that natalizumab drug levels, CD4 cell count and α-integrin levels were consistent for Q4W but levels fell with Q12W. The Committee noted that overall, variability for pharmacokinetic parameters after SC administration did not appear any greater than for IV dosing.

8.18. The Committee noted evidence of individualising the natalizumab extended dose interval based on individual trough levels in 15 patients with RRMS who switched to SC from IV natalizumab within the NEXT-MS trial (Toorop et al. J Neurol Neurosurg Psychiatry. 2023;94(6):482-6). The Committee noted that natalizumab levels were 55% lower with SC than on the IV dosing schedule and that three patients had very low levels. The Committee noted that no relapses were linked to low trough levels, however, participants had low levels for a short duration due to proactive management. The Committee noted that no ADAbs were reported. The Committee noted that the authors suggest some patients may be more vulnerable to low natalizumab drug levels with SC administration, such as those with low IV natalizumab trough levels or those on extended treatment interval dosing with a higher BMI. The Committee noted that the main reason for participants switching to SC related to difficulties with IV access and considered this was important and relevant.

8.19. The Committee noted evidence from DELIVER (101MS102), a randomised (1:1 for RRMS) open-label, multicentre study of 76 people with RRMS (*n*=76) or secondary progressive MS (*n*=52) who received 300 mg natalizumab IV or SC Q4W (Plavina et al. J Clin Pharmacol. 2016;56:1254-62). The Committee noted that a higher percentage of people receiving SC developed transient ADAbs (23%) compared with IV treatment (15%) and one participant who received SC persistently tested positive for ADAbs. The Committee considered this was a substantial difference in ADAbs development between the formulations and noted that none of the REFINE participants were reported to have tested positive for ADAbs in either group during the randomised study period (Trojano et al. 2021).

8.20. The Committee noted evidence for 64 people who either switched from natalizumab IV or started treatment with natalizumab SC, where the average combined infusion and surveillance times were 142 minutes with IV and 61 minutes with SC (Edwards et al. J Neurol Neurosurg Psychiatry. 2022;93:e2 [poster G116]). The Committee noted that 84% of people who received SC treatment reported increased convenience and 96% were satisfied or very satisfied with switching. The Committee noted that none were reported to have experienced relapses. The Committee also noted a cost analysis of SC vs IV administration of natalizumab based on patient care pathway in MS in Spain which indicated that clinic time was decreased by half with SC compared with IV administration (Torres et al. Pharmacoecon Open. 2023;7:134-41).

8.21. The Committee considered that the evidence suggested, but was not sufficiently powered to confirm, bioequivalence of natalizumab SC and IV both given Q4W in terms of pharmacokinetics and duration of effect. The Committee considered that natalizumab SC Q12W was not an appropriate regimen to use in practice.

8.22. The Committee considered that a switch from natalizumab Q6W IV to Q6W SC would not be clinically appropriate, noting an absence of data for this comparison and given concerns about low trough levels which may be insufficient to fully saturate receptors and therefore could increase risk of disease relapse or treatment failure for some

individuals. The Committee considered that people stable on natalizumab IV Q6W who would switch to SC would require Q4W dosing although there may be a difference in natalizumab trough levels between the two formulations for some individuals. The Committee therefore considered it possible that some people may experience relapse with Q4W SC compared with Q6W IV, however, it was not possible to prospectively identify all who might experience this treatment failure.

8.23. The Committee considered that people who receive natalizumab SC would require Q4W dosing regardless of whether they previously received natalizumab IV or another funded treatment for RRMS, and that Q4W dosing of natalizumab SC would be particularly important for people requiring greater disease control. Members considered that it would be reasonable to consider a switch from natalizumab IV Q6W to SC Q4W for people who have received natalizumab IV for at least six months.

8.24. The Committee noted the extension of the NOVA trial, which would compare natalizumab Q6W SC and IV for RRMS, is yet to be completed.

Suitability

8.25. The Committee noted that the application suggests supervision of SC administration for at least six months due to risk of adverse drug reaction and that subsequent treatment could be administered at home or by a caregiver. However, the Committee noted that both the natalizumab data sheet and international evidence indicate that administration would usually be performed by a healthcare professional in a clinic setting irrespective of formulation. The Committee considered that SC treatment could be given in one of several settings such as a hospital clinic (not infusion clinic) or GP clinic (eg by GP or practice nurse). However, the Committee considered that other access barriers may still apply in these settings such as the cost of a GP visit, transport requirements, travel cost, and time commitment; and considered that these barriers would be encountered more often with Q4W vs Q6W treatment.

8.26. The Committee considered that administration of natalizumab SC in a healthcare clinic would also be important to ensure timely management of other aspects of MS care for disease control and safety monitoring, such as the potential risks of progressive multifocal leukoencephalopathy and reaction to natalizumab as a biologic treatment. The Committee considered that annual MRI scans and four- or six-monthly JCV testing would occur regardless of whether an individual received natalizumab IV or SC. The Committee noted that JCV testing is easily managed when treatment is administered in a hospital clinic, however, if administered in community this testing may not be as feasible via private laboratories and/or private practices.

8.27. The Committee considered natalizumab level monitoring could be used as a tool to optimise dose intervals for individuals, or to predict and avert treatment failure due to extended interval dosing.

8.28. The Committee considered that natalizumab SC would be convenient and advantageous as an additional option especially for a subgroup of people with RRMS who have difficulty with IV access. The Committee considered that natalizumab SC would result in some overall time and healthcare resource savings, which would reduce use of hospital infusion services which are currently at capacity and would be beneficial for people with MS who may experience barriers to accessing infused treatments at hospital.

8.29. The Committee considered that the benefit of convenience with natalizumab SC would be advantageous to Māori with RRMS and may improve access to MS treatment for Māori who experience barriers to accessing infused treatments at hospital. However, the Committee noted there may be difficulties accessing a GP in remote areas and that administration at GP clinics would likely incur a cost to the person, as opposed to free hospital treatment with natalizumab IV (or SC).

8.30. The Committee considered that effective roll-out of treatment with natalizumab SC would include implementation support, GP availability in remote areas, and funding of additional visits in primary care to ensure these costs are not passed on to people with MS. However, the Committee acknowledged that barriers to access still exist in primary and secondary care and that clinic attendance for Q4W would be more frequent than current Q6W treatment.

Cost and savings

8.31. The Committee considered that the supplier's estimate of 70% of people receiving natalizumab IV switching to the SC formulation after five years, if funded, was an overestimate given the increased frequency of clinic visits with Q4W SC dosing may influence the desire to switch. The Committee considered that a maximum of 50% was a more reasonable estimate for the proportion who would switch from natalizumab IV to SC; that it would be unlikely to displace ocrelizumab usage; and that a small proportion of people might switch from other treatments for RRMS such as fingolimod or dimethyl fumarate.

8.32. The Committee noted that Q4W SC dosing would increase the pharmaceutical cost and health resource use by a third compared with Q6W IV administration, therefore savings proposed in the application would be less than indicated by the applicant.

8.33. The Committee noted that the patent for the IV formulation of natalizumab (relating to prevention or delayed progression in MS) is due to expire in 2025, and that there are biosimilars at various stages of development. The Committee considered that patent expiry should be considered and potentially be included in the economic assessment.

Funding criteria

8.34. The Committee considered it reasonable for natalizumab SC to be subject to the current MS-specific funding criteria.

Summary for assessment

8.35. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for natalizumab SC if it were to be funded in New Zealand for RRMS. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with RRMS with an EDSS score between 0 and 6.0
Intervention	Natalizumab 300 mg every four weeks via subcutaneous injection. Treatment is continued until unacceptable toxicity or disability progression past EDSS 6.0.
Comparator(s)	Natalizumab intravenous infusion administered every 6 weeks for 75% of people and every 4 weeks for 25% of people. Unlikely to displace ocrelizumab, but a small proportion of people may switch from fingolimod or dimethyl fumarate.

Outcome(s)	No difference in efficacy or safety between Q6W IV and Q4W SC (annual rate of relapse and confirmed-disease worsening). Improved efficacy relative to lower-efficacy RRMS treatments such as dimethyl fumarate and fingolimod. Improved suitability, reduced infusion burden on health system and reduced administration costs due to SC administration.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

9. Lacosamide syrup for epilepsy

Application

9.1. The Advisory Committee reviewed the application for lacosamide oral liquid for the treatment of focal epilepsy.

9.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

9.3. The Advisory Committee **recommended** that lacosamide oral liquid for the treatment of focal epilepsy be listed with a **high** priority within the context of neurology treatments, subject to similar access criteria as lacosamide tablets, but targeting access to those for whom the oral tablet formulation is unsuitable.

9.4. In making this recommendation, the Advisory Committee considered:

- The need for a suitable oral formulation for those who require treatment with lacosamide, who are unable to swallow tablets, including children under 10 years and those older than 10 years with intellectual disability, autism spectrum disorder and/or neuromuscular disability.
- There is one randomised controlled trial which provided good quality evidence showing the health benefit of lacosamide in children. However, the Committee considered that there was a lack of evidence for benefit of liquid versus tablet formulations in general.
- People who would receive the oral liquid formulation of lacosamide if one were available, would be those already dissolving lacosamide tablets.
- An oral liquid formulation of lacosamide has the potential to improve treatment adherence, and therefore seizure control, through a vastly improved taste profile.

9.5. The Advisory Committee also recommended the present Special Authority wording for lacosamide tablets be reviewed and updated, in light of developments in clinical practice and national and international guidelines.

9.6. The Advisory Committee further recommended the sequencing and lines of all funded antiseizure medicines under Special Authority be reviewed, for both children and adults with drug-resistant epilepsy.

Discussion

9.7. The discussion focused on the potential funding of a liquid formulation of lacosamide in addition to the funded tablet formulation, within the current funding treatment algorithm consequent to the Special Authorities for lacosamide and other antiseizure treatments. The specific place of lacosamide and other anti-epileptic treatments funded under Special Authority was not reviewed at this stage.

Māori impact

9.8. The Committee discussed the impact of funding a liquid formulation of lacosamide for the treatment of drug-resistant focal epilepsy on Pharmac's Hauora Arotahi (Māori health areas of focus) and Māori health outcomes.

9.9. The Committee noted that epilepsy is not considered to be a part of Pharmac's Hauora Arotahi (Māori health areas of focus) and that Māori experience different health outcomes when compared with non-Māori.

9.10. The Committee noted Māori aged 18 years and younger have a similar unadjusted prevalence of treated epilepsy to Europeans in New Zealand. The Committee also noted that after adjustment for socioeconomic deprivation, Māori children had a lower prevalence of epilepsy compared to European children (Ali et al. Neurology. 2021;97:e1933-41).

9.11. The Committee was made aware of several epidemiological peer reviewed observational cohort studies and national health reports, with data suggesting Māori experience a higher degree of epilepsy burden compared to the New Zealand European population with epilepsy due to:

- increased emergency presentations in adults with epilepsy (Joshi 2015; Lance 2017)
- increased admissions for epilepsy or status epilepticus in children (Craig 2014; Simpson 2018)
- higher rates of rate of re-presentation to hospital (Hamilton et al. Epilepsia. 2020;61:519-29).increased rates of hospitalisation for status epilepticus (29.31 per 100,000 per year reported for Māori compared to 19.13 per 100,000 per year for Europeans) (Bergin et al. Epilepsia. 2019;60:1552-64)
- being less likely to receive immediate antiseizure medications (Hamilton et al. 2020)
- being more likely to remain untreated (P=0.024) (Hamilton et al. 2020)
- having higher mortality rates (hazard ratio 1.41, 95% CI 1.08 to 1.83). (Hamilton et al. 2020).

9.12. The Committee noted that focal epilepsy does not fall under any of the Hauora Arotahi.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system

9.13. The Committee considered the impact of focal epilepsy on Pacific peoples, disabled people, and other populations who experience inequities.

9.14. The Committee noted that Pacific individuals aged 18 and younger had a similar unadjusted prevalence of treated epilepsy compared to Europeans in New Zealand. The Committee also noted that after adjustment for socioeconomic deprivation, Pacific peoples had a lower prevalence of epilepsy compared to European children (Ali et al. 2021). The Committee also noted that Pacific peoples experienced higher rates of hospitalisation for status epilepticus compared to New Zealand Europeans,

with rates of 26.55 per 100,000 per year compared to 19.13 per 100,000 in Europeans reported in an observational study conducted in Auckland (Bergin et al. 2019).

9.15. The Committee noted that epilepsy may co-present with intellectual disability, and in some types of epilepsy the seizures, and abnormal electrical activity in the brain between seizures, has a negative impact on the developing brain resulting in additional cognitive impairment (ie Developmental and Epileptic Encephalopathy). The Committee considered, that based on a population based epidemiological study (Poke et al. Neurology. 2023;100:e1363-75), there could be approximately 2300 individuals aged 16 and younger in New Zealand with development impairment and epilepsy, including approximately 1500 with developmental and epileptic encephalopathies, and approximately 840 with intellectual disability and epilepsy

9.16. The Committee noted that people living in more socioeconomically deprived areas in New Zealand have a higher prevalence of epilepsy compared to people living in less deprived areas. The Committee noted that the prevalence of treated epilepsy was 1.9 times as high among people living the most deprived quintile areas in New Zealand compared to people living in the least deprived quintile (rate ratio 1.9, 95% CI 1.6 to 2.2) (Ali et al. Neurology. 2021;97:1933-41).

Background

9.17. The Committee noted that lacosamide tablets are currently listed on the Pharmaceutical Schedule, subject to Special Authority criteria, as a sixth-line treatment for people with focal epilepsy (formerly known as partial-onset epilepsy), and seizures not adequately controlled by, or experiencing unacceptable side effects from, optimal treatment with all of the following: sodium valproate, topiramate, levetiracetam, and any two of carbamazepine, lamotrigine, and phenytoin sodium.

9.18. The Committee noted that in November 2015, the Neurological Subcommittee (now Neurological Advisory Committee) recommended listing of the tablets be extended to include fifth-line epilepsy treatment with a medium priority. The Committee noted that when making this recommendation, the Subcommittee considered that lacosamide tablets would be clinically useful if they were used fifth-line for drug-resistant epilepsy as they were generally well tolerated and less time-consuming to initiate people on than some other oral tablet treatments, for example carbamazepine and phenytoin. The Committee noted that in February 2022, PTAC accepted the Neurological Subcommittee's 2015 recommendation. The Committee noted its November 2015 (as a Subcommittee) deliberations did not specifically consider lacosamide treatment in childhood epilepsy, and there was unable to be formal paediatric neurology specialist input into that discussion at that time.

9.19. The Committee noted that Pharmac currently funds 16 antiseizure medicines in the Control of Epilepsy Therapeutic Group, 13 of which are funded without restriction.

9.20. The Committee noted that the brand of the oral liquid being considered in the application was Te Arai Biofarma Limited Lacosamide oral liquid 10 mg/ml. The Committee noted that the originator brand Vimpat became off patent in 2022.

9.21. The Committee noted that this application requested that lacosamide oral liquid be funded as fourth-line antiseizure medication for adults with focal epilepsy and third-line antiseizure medication for children with focal epilepsy.

Health need

9.22. The Committee noted that epilepsy is a group of disorders that are characterised by the predisposition to have recurrent seizures (Scheffer et al. Epilepsia. 2017;58:512-21)

9.23. The Committee noted that active epilepsy is defined as ongoing seizures or being on antiseizure medication. The Committee noted that there is limited epidemiological evidence on the prevalence of active epilepsy in New Zealand adults, but the global estimates of active epilepsy range between 4 to 10 per 1000 people (Fiest et al. Neurology. 2017;88: 296-303). The Committee noted that a recent cross-sectional epidemiological study conducted in New Zealand reported the one-year period prevalence of treated epilepsy to be 3.4 per 1000, among individuals aged 18 and younger (Ali et al. 2021).

9.24. The Committee noted that health need of people with focal epilepsy has previously been discussed by PTAC in its discussions for the use of other antiseizure medications for use in focal epilepsy, including in February 2020, in the context of perampanel, and August 2020, in the context of zonisamide.

9.25. The Committee noted approximately 70% of people with epilepsy have focal epilepsy (Tan et al. Epilepsia. 2018;60:518-26). People with focal epilepsy have focal seizures, however there are many different types of focal epilepsy, each with specific evidenced based treatment protocols (Wirrell et al. Epilepsia. 2022;63:1333-48). The Committee noted that people with epilepsy have a high number of associated comorbidities and that these should be considered when choosing antiseizure medications, to avoid harm(Scheffer et al. Epilepsia. 2017;58:512-21).

9.26. The Committee was informed that clinical drug trials tend to focus on seizure types and not epilepsy syndromes. The Committee considered that the choice of antiseizure medication for people with focal epilepsy should be based not only on seizure type but also on the type of focal epilepsy syndrome, the aetiology of the epilepsy, the individual's specific comorbidities, and their demographic characteristics (ie age, sex, childbearing potential) (Asadi-Pooya et al. Epilepsia. 2022;63:254-5). The Committee considered that most people with epilepsy will experience seizure freedom with currently funded antiseizure medications, but there were some individuals for whom their seizures are drug-resistant to currently funded antiseizure medications or their comorbidities, or specific demographic group make trialling some of the funded antiseizure medications clinically inappropriate.

9.27. The Committee noted the International League Against Epilepsy (ILAE) definition of drug -resistant epilepsy was the failure of two tolerated and appropriately chosen and used antiseizure medications to achieve sustained seizure freedom. The Committee considered that drug-resistant epilepsy impacts people's health-related quality of life in terms of stigma, discrimination, the ability to carry out usual activities such as driving and employment, as well as effects on relationships (Peruccca et al. Lancet Neurol. 2023;22:723-34). The Committee noted that drug-resistant epilepsy is also associated with increased morbidity relating to increased accidents and increased mental health comorbidities (Fattorusso et al. Front Neurol. 2021:674483, Mahler et al. Neurology. 2018;90:e779-89). The Committee noted that in the developmental and epileptic encephalopathies, drug-resistant epilepsy is associated with worse long-term cognitive and seizure outcomes. The Committee considered having uncontrolled seizures also makes it difficult for families to find respite care for these children. The Committee noted that some seizures in focal epilepsy, such as tonic-clonic seizures, are associated with an increased risk of mortality (Sveinsson et al. Neurology. 2019;94: e419-e429).

9.28. The Committee considered that there is currently an unmet health need in those who require treatment with lacosamide, who are unable to swallow tablets whole and require the tablets to be crushed and dissolved. The Committee understood that children under 10 years and those older than 10 years with intellectual disability, autism spectrum disorder and/or neuromuscular disability were most likely to experience difficulty swallowing tablets. The Committee noted that paediatric

pharmacists in main centres in New Zealand recommend to community pharmacists that the tablets can be crushed, and put in yoghurt or dissolved in water, which is in line with the AusDI recommendation. Members noted that the crushed tablets have an extremely unpalatable taste profile, which may affect treatment adherence.

9.29. The Committee noted again:

9.29.1. That Māori aged 18 years and younger have been reported having a similar unadjusted prevalence of treated epilepsy to New Zealand Europeans, but adjusting for socioeconomic deprivation resulted in Māori children having a lower prevalence than NZ European children (Ali et al. 2021)

9.29.2. Māori have experienced higher rates of hospitalisation for status epilepticus compared to New Zealand Europeans, with rates of 29.31 per 100,000 per year reported for Māori compared to 19.13 per 100,000 per year for Europeans reported in an observational study conducted in Auckland (Bergin et al. 2019)

9.29.3. An observational study reporting that Māori with newly diagnosed epilepsy were less likely to receive treatment for epilepsy compared to the New Zealand general population (*P*=0.024) (Hamilton et al. 2020)

9.29.4. Māori with newly diagnosed epilepsy have had higher mortality rates than non-Māori (hazard ratio 1.41, 95% CI 1.08 to 1.83). This is reported to be due to a combination of barriers to adequate treatment for epilepsy, and a greater burden of comorbidities (Hamilton et al. 2020).

9.30. The Committee also noted again that:

9.30.1. Pacific individuals aged 18 and younger had a similar unadjusted prevalence of treated epilepsy compared to NZ Europeans, but adjusting for socioeconomic deprivation resulted in Pacific children having a lower prevalence than NZ European children (Ali et al. 2021).

9.30.2. Pacific peoples experienced higher rates of hospitalisation for status epilepticus compared to New Zealand Europeans, with rates of 26.55 per 100,000 per year compared to 19.13 per 100,000 in Europeans reported in an observational study conducted in Auckland (Bergin et al. 2019).

9.30.3. People living in more socioeconomically deprived areas in New Zealand have a higher prevalence of epilepsy compared to people living in less deprived areas. The Committee noted that the prevalence of treated epilepsy was 1.9 times as high among people living the most deprived quintile areas in New Zealand compared to people living in the least deprived quintile (rate ratio 1.9, 95% CI 1.6 to 2.2) (Ali et al. 2021).

9.31. The Committee noted that epilepsy may co-present with intellectual disability, and in some types of epilepsy the seizures, and abnormal electrical activity in the brain between seizures, may have a negative impact on the developing brain resulting in additional cognitive impairment (ie developmental and epileptic encephalopathy). The Committee considered, that based on epidemiological information from Wellington (Poke et al. 2023), there could be approximately 2300 individuals aged 16 and younger in New Zealand with development impairment and epilepsy, including approximately 1500 with developmental and epileptic encephalopathies, and approximately 840 with intellectual disability and epilepsy.

Health benefit

9.32. The Committee noted that the Vimpat brand of lacosamide oral liquid is approved by Medsafe for use as a monotherapy in the treatment of focal onset seizures in people with epilepsy aged 16 years and older, as an add-on therapy in the treatment of focal

onset seizures in people with epilepsy aged 4 years and older, and as an add-on therapy in the treatment of generalised onset tonic-clonic seizures in people with genetic generalised epilepsy (previously idiopathic generalised epilepsy) aged 4 years and older. The Committee noted that focal onset seizures were previously termed partial-onset seizures and include focal onset seizures that spread to become focal to bilateral tonic-clonic seizures, which members considered preferable wording.

9.33. The Committee noted that the Te Arai Biofarma Limited brand lacosamide oral liquid did not have Medsafe approval at the time of the meeting, including specifically for focal onset seizures.

9.34. The Committee noted that the health benefit of lacosamide as a pharmaceutical has previously been described by the Neurological Subcommittee in November 2015, members noting there was unable to be formal paediatric neurology specialist input into that discussion at that time.

9.35. The Committee noted the results of the randomised, controlled, Phase 3 clinical trial describing the health benefit of lacosamide specifically in children (Farkas et al. Neurology. 2019;93:e1212-16). The Committee noted that participants received the oral liquid formulation of lacosamide if they weighed less than 50 kg, and tablets if they weighed over 50 kg. The Committee considered that the trial showed similar efficacy and safety in children as in the adult randomised controlled trials, and showed lacosamide was generally well tolerated by children. The Committee considered this trial was good quality evidence showing the health benefit of lacosamide in children. However, the Committee considered that there was a lack of evidence for efficacy benefit of liquid versus tablet formulations in general. The Committee considered that palatability and reduced volume required to swallow for the oral liquid in comparison to dissolved tablets were important factors to consider when assessing health benefit through the possibility of increasing treatment adherence. The Committee noted that the oral liquid formulation of lacosamide is currently funded in Australia, Canada, and Scotland.

Suitability

9.36. The Committee noted the enhanced suitability of an oral liquid formulation of lacosamide for people who cannot swallow tablets or have difficulty swallowing tablets, due to a possibly improved taste profile and lower volume required to swallow compared to dissolved lacosamide tablets. The Committee considered that the oral liquid formulation is likely to have an improved taste profile due to the sweetening excipients.

9.37. The Committee noted that, for people who cannot swallow whole tablets, the current administration method of crushing and dissolving lacosamide tablets may be associated with various suitability issues. The Committee considered that this creates difficulties in achieving accurate dosing and is time consuming, noting that the tablets take approximately five minutes to dissolve in water. The Committee considered that the unpleasant taste of the crushed tablets may affect treatment adherence.

9.38. The Committee considered that an oral liquid formulation of lacosamide has the potential to improve treatment adherence, and therefore seizure control, through a vastly improved taste profile. The Committee considered that people are more likely to receive the prescribed dose, as dosing accuracy is much improved with the liquid, and that measuring a liquid provides an easier administration method for busy families than dissolving a tablet.

9.39. The Committee considered oral liquid and tablet formulations of lacosamide to be bioequivalent, and thus did not express any concerns with regard to seizure control when switching between the two formulations.

9.40. The Committee noted that lacosamide oral liquid has a shelf life of three years and should be discarded within two months of opening and should be stored at room temperature. However, the Committee considered that at the recommended doses, each bottle was unlikely to last an individual more than two months, and so did not consider this to be a concern.

Cost and savings

9.41. The Committee considered that people who would receive the oral liquid formulation of lacosamide, if one were available, would be those who are currently receiving dissolved lacosamide tablets. The Committee considered it very unlikely that people receiving other antiseizure medications would switch to receiving lacosamide oral liquid if they were adequately managed on those other antiseizure medications.

9.42. The Committee understood that dispensing patterns for oral liquid presentations of antiseizure medications have a distinct age-related pattern, with the youngest age groups having the highest percentages of dispensing being for oral liquid presentations. The Committee considered that it reasonable to assume that uptake of lacosamide oral liquid, relative to lacosamide tablets, is likely to vary by age in a similar way to what has been observed for levetiracetam oral liquid relative to levetiracetam tablets.

9.43. The Committee considered that uptake of lacosamide liquid would peak rapidly due to this treatment being relatively familiar to relevant prescribers as well as a lack of a requirement to titrate when converting between the different formulations of lacosamide.

9.44. The Committee considered that the people most likely to receive lacosamide oral liquid, if it were to be funded, would be individuals under 10 years of age who are unable to swallow tablets, as well as individuals over 10 years with intellectual disabilities, autism spectrum disorder, neuromuscular difficulties who are unable to swallow tablets, and individuals who are using gastronomy tubes.

Funding criteria

9.45. The Committee noted that the current funding criteria for lacosamide tablets provide funded access to people with focal epilepsy whose seizures are not adequately controlled by, or the person has experienced unacceptable side effects from, optimal treatment with all of the following: sodium valproate, topiramate, levetiracetam, and any two of carbamazepine, lamotrigine, and phenytoin sodium (ie sixth-line treatment). The Committee noted that current Special authority do not include criteria for age or poly/monotherapy treatment status.

9.46. Members considered the Special Authority requirements for lacosamide tablets should be reviewed and updated.

9.47. The Committee considered it would be appropriate to target funded access of lacosamide oral liquid to those who are unable to swallow tablets.

Summary for assessment

9.48. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for lacosamide oral liquid if it were to be funded in New Zealand for focal epilepsy. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People over 4 years of age with drug-resistant focal epilepsy who are unable or have difficulty swallowing the tablet formulation and have experienced insufficient benefit or unacceptable side effects from optimal funded treatment.
Intervention	Lacosamide oral liquid, at an appropriate dose for weight as per the Medsafe Datasheet for Vimpat
Comparator(s) (NZ context)	Lacosamide tablets, at an appropriate dose for weight as per the Medsafe Datasheet for Vimpat
Outcome(s)	Lacosamide oral liquid and lacosamide tablets are bioequivalent, and as such there is expected to be no difference in benefits or risks between the two formulations

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

10. Erenumab, galcanezumab, and atogepant for chronic and episodic migraine

Application

10.1. The Advisory Committee reviewed applications for:

- 10.1.1. erenumab in the treatment of chronic migraine
- 10.1.2. erenumab in the treatment of episodic migraine
- 10.1.3. galcanezumab in the treatment of chronic migraine
- 10.1.4. galcanezumab in the treatment of episodic migraine
- 10.1.5. atogepant in the treatment of chronic migraine
- 10.1.6. atogepant in the treatment of episodic migraine.

10.2. The Advisory Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

10.3. The Committee also reviewed the health need and health benefit of treatments associated with cluster headaches. The Committee noted that at the time of this meeting Pharmac had not received a funding application for the treatment of cluster headaches, and the Advisory Committee has made no recommendations for this indication.

Recommendation

10.4. The Advisory Committee **recommended** that erenumab, galcanezumab, and atogepant for chronic migraine be listed with a **high** priority within the context of neurology treatments, subject to the following Special Authority criteria:

CGRP antagonists – Chronic migraine
Initial application from a relevant practitioner. Approval valid for 3 months.
Both:
1. Individual has chronic migraine defined as experiencing at least 15 headache days per month (with at least 8 days having headache with migraine features), for at least 3 months; and
2. Both:
   2.1 Migraine disease is refractory to at least three funded prophylactic agents; or
   2.2 Funded prophylactic treatments are clinically unsuitable or not tolerated.

Renewal from a relevant practitioner. Approval valid for 6 months.
1. Improvement in number of migraine days per month of at least 30% compared with baseline.

10.5. The Advisory Committee **recommended** that erenumab, galcanezumab, and atogepant for episodic migraine be listed with a **high** priority within the context of neurology treatments, subject to the following Special Authority criteria:

CGRP antagonists – Episodic migraine
Initial application from a relevant practitioner. Approval valid for 3 months.
Both:
1. Individual has episodic migraine defined as experiencing at least 4 headache days per month and less than 15 headache days, for at least 3 months; and
2. Both:
   2.1 Migraine disease is refractory to at least three funded prophylactic agents; or
   2.2 Funded prophylactic treatments are clinically unsuitable or not tolerated.

Renewal from a relevant practitioner. Approval valid for 6 months.
1. Improvement in number of migraine days per month of at least 50% compared with baseline.

10.6. The Advisory Committee considered the following in making these recommendations:

- The higher health need of people with chronic migraine (CM) compared to people with episodic migraine (EM).
- Unmet need for people with migraine (CM or EM) due to lack of migraine specific treatments.
- Limited access to neurology or migraine specialist care within the publicly funded health system.
- The benefit of calcitonin gene related peptide (CGRP) antagonist treatments (erenumab, galcanezumab, or atogepant) being similar in terms of reduction of monthly headache or migraine days.

Discussion

Migraine Foundation Aotearoa New Zealand

10.7. The Migraine Foundation Aotearoa New Zealand presented to the Committee and Pharmac staff on the impact and burden of living with migraine in New Zealand. The Migraine Foundation is a volunteer organisation advocating and supporting people with migraine in New Zealand.

10.8. The Migraine Foundation discussed a survey they conducted on the impact of migraine on people with migraine in New Zealand. Some of the key results highlighted to the Committee were the significant impacts on daily life from migraine, with estimated self-rated health lower than the general public's in people with migraine.

10.9. The Migraine Foundation highlighted the impact of migraine on people's mental health and the stigma and isolation that people with migraine experience due to a lack of the understanding of migraine as a medical condition.

10.10. The Migraine Foundation discussed the inaccessibility of public specialist care and the challenges for people that live rurally, and how this means people present to emergency departments or primary care more often with acute migraine.

10.11. The Migraine Foundation relayed people's experiences of current preventatives that were not specifically designed for migraine and the resulting disappointment if these treatments are not effective or have intolerable side effects. The Migraine Foundation explained that after multiple trials of preventatives people lose faith in preventative treatments and therefore are nervous to try new medications.

Māori impact

10.12. The Committee discussed the impact of funding erenumab, galcanezumab, or atogepant for the treatment of EM or CM on Pharmac's Hauora Arotahi (Māori health areas of focus) and Māori health outcomes.

10.13. The Committee noted that EM and CM are not considered to be a part of the Hauora Arotahi.

10.14. The Committee noted that Māori were reported to be affected by migraine at a similar prevalence to the overall population in the New Zealand Health Survey. The Committee noted a 1993 study in South Auckland that reported there was no difference in doctor attendance for headaches, but people of NZ European ethnicity were more likely to have their headaches diagnosed as migraine (Thomson & West. N Z Med J. 1993;106:477-80).

10.15. The Committee considered that there is a likely a greater unmet need in primary care for Māori. The Committee noted that despite Māori experiencing chronic pain at a higher rate than other ethnicities, Māori have a lower rate of accessing chronic pain services (Devan et al. NZ Med J. 2021;134:19-29).

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been underserved by the health system

10.16. The Committee discussed the impact of funding migraine treatments on Pacific, disabled, and underserved populations.

10.17. The Committee considered that there was no significant difference in prevalence of migraine in Pacific peoples compared to other ethnicities.

10.18. The Committee noted that women experience higher rates of migraine, disability, emergency department use and are more restricted in the treatments than can be used, particularly for those women of childbearing potential, compared to men.

10.19. The Committee considered that access to publicly available neurological services is poor. The Committee considered that for rural populations that this access is further limited due to limited neurological specialist care resource in these areas, as most are located in tertiary hospitals.

Background

10.20. The Committee noted that PTAC reviewed the application for erenumab for CM at its August 2021 meeting. The Committee noted that the application received from PTAC a low priority recommendation at that time. The Committee noted that PTAC also recommended that erenumab be considered for acute/episodic migraine (EM). The Committee noted that neither galcanezumab nor atogepant had been previously considered by PTAC for any indication.

Health need

10.21. The Committee noted that the International Headache Society definition of migraine is an acute condition that lasts 4 to 72 hours, with at least two of the following: unilateral, pulsating, moderate or severe intensity, aggregation by or causing

avoidance of routine physical activity, and at least one of the following: nausea and vomiting, photophobia and phonophobia, not better accounted for by another diagnosis. The Committee noted that 20-30% of people may have aura, that is, reversible neurological symptoms lasting 5 to 10 minutes prior to the headache phase.

10.22. The Committee noted that CM is defined as more than 14 headache days per month, at least 8 days with typical migraine features and lasting more than 3 months. The Committee considered that 12% of people with migraine have CM (Lipton et al. Headache. 2022;62:122-40). The Committee considered that people with EM can transform to those with CM and reverse. The Committee noted the CaMEO study, which estimated that 26% of people remit from CM to EM over the study period of 15 months (Serrano et al. J Headache Pain. 2017;18:10). The Committee noted that it was reported that 7.6% of people with EM at baseline fulfilled criteria for CM over the succeeding 15 months (Serrano et al. 2017).

10.23. The Committee noted that PTAC considered the prevalence of migraine to be 15.5% in New Zealand. The Committee noted that the New Zealand Health Survey 2006/7 had estimated prevalence as 13% in women and 5.5% in men. The Committee considered that the estimated prevalence of CM was 1.8% of adults in New Zealand as previously considered by PTAC in August 2021. The Committee noted that in the Global Burden of Disease Study that migraine was the top cause of years lived with disability (YLD) in people aged 15 to 49 years, and in New Zealand was fourth cause of YLD with an impact similar to major depressive disorder. The Committee noted that the peak ages for migraine are 18-29 years and 40-49 years. The Committee noted that migraine disease affects females more than males, at an estimated ratio of 2-3 female to every male. The Committee noted the England/Wales National Institute of Clinical Excellence (NICE) assessment of erenumab for chronic migraine, reviewed by PTAC, which estimated the EQ5D health utility of migraine disease to be 0.466, lower than that of type 2 diabetes using insulin (utility: 0.66), giving a sense of the magnitude of quality of life loss with migraine (NICE. Erenumab technology appraisal guidance TA682. 2021).

10.24. The Committee considered that people with CM have higher disability, lower household income, low rates of full-time employment, more comorbidities, and higher use of healthcare. The Committee noted the results of the Migraine Foundation Aotearoa New Zealand survey 2022 describing the impact of CM and EM on people in New Zealand, in particular:

- 87% of respondents with CM and 37.5% with EM in the survey reported experiencing severe disability.
- 16% of respondents with CM and 4% with reported poor self-rated health.
- 67% of respondents with CM and 14% with EM reported medication overuse.

10.25. The Committee noted that the survey was a self-selected sample and that the proportion of CM compared to EM was not the same as predicted based on population studies. The Committee considered that 9% of all people with migraine have CM, contrasting with 20% of respondents reporting having CM in the survey.

10.26. The Committee noted results from the Dunedin Multidisciplinary Health and Development Study phase 26 (ie aged 26 years) assessment, where 39% of those with migraine reported impaired work quite a lot to very much and 42% experienced impaired social activities (Waldie & Poulton. Headache. 2002;42:612-9).

10.27. The Committee noted submissions from people with migraine describing their lived experience of severe migraine related disability and suffering and for them the inadequacy and unsuitability of currently funded treatments.

10.28. The Committee noted that PTAC considered that people who have tried at least three preventative medicines and still experience migraine attacks have an unmet health need.

10.29. The Committee noted that PTAC considered that 28% of people with migraine take preventative treatment and that 9% of people with migraine would find three or more treatments ineffective, as based on a NICE assessment (NICE. Erenumab technology appraisal guidance TA682. 2021). The Committee noted that the NICE assessment estimated that 19% of people with migraine experienced three or more treatments ineffective.

10.30. The Committee considered that the impact on partners, children, and family and whānau included the stress of caring for someone with this condition, as well as the person with migraine missing social activities they would otherwise be able to participate in. The Committee considered that this is supported by local and international evidence.

10.31. The Committee considered that Māori were reported to be affected by migraine at a similar prevalence to the overall population in the New Zealand Health Survey. The Committee noted a 1993 study in South Auckland that reported there was no difference in doctor attendance for headaches but people of European ethnicity more likely to be diagnosed as migraine (Thomson & West. N Z Med J. 1993;106:477-80). The Committee considered that there is a likely a greater unmet need in primary care for Māori. The Committee noted that despite Māori experiencing chronic pain at a higher rate than other ethnicities, Māori have a lower rate of accessing chronic pain services (Devan et al. N Z Med J. 2021;134:19-29).

10.32. The Committee considered that there was no significant difference in prevalence of migraine in Pacific peoples compared to other ethnicities. The Committee noted that women experience higher rates of migraine, disability, emergency department use, and are more restricted in the treatments than can be used, particularly for those of childbearing potential, compared to men.

10.33. The Committee noted that cluster headache is a rare headache disorder affecting up an estimated 0.1% of the population, based on a meta-analysis of population study estimates (Fischera et al. Cephalalgia. 2008:614-8). The Committee noted that the attacks occur in series lasting weeks or months with remission for months or years with 10-15% of those with cluster headaches having chronic cluster headaches without remission. The Committee noted that the pain experienced in cluster headaches occurs on one side of the head orbitally, supraorbitally, temporally, or a combination, and the pain can be excruciating with people unable to lie down and so people pace the floor. The Committee noted that cluster headaches usually start at around 20 to 40 years of age, men are three time more likely to be affected than women, and a very high prevalence of present or past tobacco smoking (90% of people with cluster headaches) (Joshi et al. J Headache Pain. 2017;18:76). The Committee considered that diagnosis is often delayed, and also that cluster headache diagnostic criteria are very strict and this could lead to underdiagnosis compounded by limited specialist access available in the New Zealand public system. The Committee noted acute treatments include subcutaneous sumatriptan, high flow oxygen, and/or non-invasive vagal nerve stimulation; preventative treatments include verapamil, lithium, melatonin, or topiramate; and interim treatments include oral prednisone and greater occipital nerve block (with corticosteroids). The Committee considered that this is a small but high need population.

10.34. The Committee considered that access to publicly available neurological services is poor and most people with migraine are managed in primary care. The Committee considered that most referrals reported as “accepted” by Te Whatu Ora included virtual clinic assessments that result in a note being sent to the GP or primary care

practitioner with simple advice or direction to consult standard treatment guidelines (eg Health Pathways) rather than a specialist outpatient clinic assessment. The Committee considered that for rural populations that this access is further limited due to limited neurological specialist care resource in these areas, as most services are located in tertiary hospitals.

Health benefit

10.35. The Committee noted that all treatments considered inhibited the CGRP pathway. The Committee noted that CGRP is a vasodilatory neuropeptide released by activated perivascular trigeminal nerves in migraine that then contributes to neurogenic inflammation, with further CGRP release in what becomes an escalating positive feedback loop.

10.36. The Committee noted that galcanezumab is an anti-CGRP monoclonal antibody, erenumab is an anti-CGRP receptor monoclonal antibody, and atogepant is a small molecule CGRP receptor blocker.

10.37. The Committee considered that the current acute treatments for migraine include non-steroidal anti-inflammatories (NSAIDs) (eg diclofenac, ibuprofen, naproxen) and triptans (sumatriptan and rizatriptan). The Committee noted that NSAIDs have gastrointestinal and cardiovascular side-effects that make them intolerable or contraindicated for some people. The Committee noted that triptans cannot be used in people with coronary or peripheral vascular disease due to risk of vasospasm. The Committee noted that these treatments are limited in their use (two sumatriptan doses and three rizatriptan doses in 24 hours) and carry the risk of overuse. The Committee considered that preventative treatment is recommended when migraine occurs more than six days per month or four days with impairment a month or three days per month with severe impairment.

10.38. The Committee considered that chronic migraine can be prevented or reversed with effective treatment of attacks, avoidance of overuse of triptans and opioids, and early use of effective prevention.

10.39. The Committee considered current preventative treatments for migraine include beta-blockers (propranolol, metoprolol, or nadolol), amitriptyline, topiramate, pizotifen, valproate, carbamazepine, and botulinum toxin injections. The Committee considered that these agents were unsatisfactory for prevention of migraine, with high discontinuation rates due to poor tolerability and efficacy. The Committee considered that trials of these treatments require slow dose titration with trials being 8 to 12 weeks duration and if effective, gradual withdrawal after 6 to 12 months use. The Committee considered that most treatments are unsuitable for people of childbearing potential, in particular valproate and topiramate.

Chronic migraine

10.40. The Committee noted a 16-week double-blind trial comparing topiramate 100 mg daily and placebo in 306 people with CM who had previously experienced treatment failure with two or less other preventative medications, not including topiramate. The Committee noted that only 55% of people completed the trial with 10.9% discontinuing due to adverse effects in the treatment group and 6.1% discontinuing in the placebo group. The Committee noted that the reported reduction in headache days in the last month was 6.4 days in the topiramate group and 4.7 days in the placebo (*P*=0.01) (Silberstein et al. Headache. 2007;47:170-80). The Committee considered that while topiramate is considered to be the more effective of currently funded options, its efficacy is limited in migraine prevention.

10.41. The Committee considered that botulinum toxin injections are not routinely used in the public system as the demand is overwhelming and the administration of the treatment is time intensive. Members noted that in some regions the demand was so

high that the service is restricted to those already receiving treatment and no new people are able to be treated. The Committee considered that for this reason botulinum toxin injections are not an appropriate comparator for use in CM economic assessments.

10.42. The Committee noted the PREEMPT I trial assessing botulinum toxin injections compared to placebo for treating CM with the outcome of mean change of in frequency of headache days from baseline at week 24, reported as -8.4 vs -6.6 (*P*<0.001) (Aurora et al. Cephalalgia. 2010;30:793-803). The Committee considered that while this benefit was significant statistically, clinically the benefit was only modest and that overall botulinum toxin is not a particularly effective treatment for CM.

10.43. The Committee considered evidence from the Study 275 (Tepper et al. Lancet Neurol. 2017;16:425-34). The Committee noted that Study 275 was a double-blind, phase 2, 12-week trial in people with CM (*N*=667) comparing erenumab 70 mg, 140 mg, and placebo. The Committee noted that the mean month change in migraine days compared to placebo was -6.6 days with either dose compared to placebo which was -4.2 days, a difference of -2.5 days (95% CI -3·5 to -1·4, *P*<0·0001) for each dose. The Committee considered that this study suggests the 70 mg and 140 mg doses to be closely comparable and with no evidence for a larger effect in the 140 mg group.

10.44. The Committee considered the 52 week open-label extension of Study 275 assessing erenumab in people with CM (Tepper et al. Cephalalgia. 2020;40:543-53). The Committee noted that 74.1% of participants completed the extension of the trial. The Committee noted at completion of the study the reduction in mean migraine days was -9.3 days (95% CI, -10.0, -8.6) in the erenumab 70 mg and 140 mg group. The Committee considered that this reduction would be clinically significant for a person with CM as they have, at minimum, 15 headache days a month. The Committee noted that in the erenumab 70 mg group the reduction in monthly migraine days was -10.0 days (95% CI, -10.9, -9.0) and in the erenumab 140 mg group was -10.5 days (95% CI, -11.5, -9.4). The Committee considered that there was likely not a larger effect in the 140 mg group compared to the 70 mg group for people with CM.

10.45. The Committee considered evidence from REGAIN (Detke et al. Neurology. 2018;91: e2211–21) and CONQUER (Mulleners et al. Lancet Neurol. 2020;19:814-25) randomised controlled trials of galcanezumab in CM.

10.45.1. The Committee noted that the mean change in number of monthly migraine days in people with CM (*N*=1,113) in REGAIN using placebo -2.7 days and those treated with galcanezumab 120 mg -4.8 days and treated with galcanezumab 240 mg -4.6 days with a difference of −2.1 days (95% CI –2.9 to –1.3, *P*<0.001) and –1.9 days (95% CI −2.7 to −1.1, *P*<0.001), respectively.

10.45.2. The Committee noted the mean change in number of monthly migraine days in people with CM treated with 240 mg galcanezumab loading dose and then 120 mg monthly thereafter in the CONQUER trial where the difference between placebo and treatment groups was -3.7 days (95% CI -3.4 to -1.7; *P*<0.0001). The Committee considered both trials suggest that galcanezumab has an effect over placebo.

10.45.3. The Committee noted the 1-year open label extension of the REGAIN trial including people with CM. All participants were treated with one month of galcanezumab 240 mg then one month of galcanezumab 120 mg followed by flexible dosing (Pozo-Rosich et al. Curr Med Res Opin. 2022;38:731-42). The Committee considered that over this period, people on treatment tended to continue to improve in reduction of monthly migraine days regardless of the

group (placebo or galcanezumab 120 mg or galcanezumab 240 mg) they were initially randomised to.

10.45.4. The Committee noted the patient-reported outcomes from the 1-year open label extension REGAIN trial (Ford et al. Qual Life Res. 2021; 30:105-15). The Committee considered that participants patient-reported outcomes (Migraine-Specific Quality of Life [MSQ]) continued to improve over the study extension period.

10.45.5. The Committee noted the CONQUER trial open label extension follow up and quality of life data relating to the use of galcanezumab in CM and EM:

- Reuter et al. Adv Ther. 2021;38:5465-83
- Tepper et al. Clin Drug Investig. 2022; 42: 263–75

10.46. The Committee considered evidence from the unpublished PROGRESS trial (NCT0855137) assessing atogepant in people with CM (*N*=694). The Committee noted the change in mean headache days in the atogepant 60 mg group was -6.88 (95% CI -7.67, -6.08) and in placebo group was -5.05 (95% CI -5.86, -4.25). The Committee considered that atogepant was effective in people with CM.

10.47. The Committee considered an indirect treatment comparison of the three agents in CM undertaken by the supplier of atogepant. The Committee noted that this comparison reported that there was no difference in the mean monthly headache days or acute medication use days. The Committee noted the secondary outcome in all of the trials was a reduction by 50% mean headache days and this is included in the PTAC-recommended Special Authority renewal criteria. The Committee considered that in people with CM that an estimated 30-40% would respond with a 50% reduction in mean headache days.

10.47.1. The Committee considered that the trials were comparable, potentially due to the study populations being similar in each. The Committee noted that there was little data in men and that participants mostly were aged around 40 years, but nonetheless considered that men and younger people would be just as likely to respond to treatment as those people demonstrated in the trials.

Episodic migraine

10.48. The Committee considered an unpublished meta-analysis provided in a supplier application collating results from the ARISE (Dodick et al. Cephalalgia. 2018;38:1026-37), LIBERTY (Reuter et al. Lancet. 2018;392:2280-7) and STRIVE (Goadsby et al. N Engl J Med. 2017;37:2123-32) trials of the monthly acute migraine medication use days in EM when using erenumab. The Committee considered that the effect of erenumab seemed to vary depending on dose (70 mg vs 140 mg erenumab). The Committee considered that there could be differences in the effect of erenumab in people with EM dependent on the dose. The Committee considered that 40-60% of people with EM are likely to reach the 50% reduction in monthly headache days.

10.49. The Committee considered the 52-week open label extension of the STRIVE trial (Goadsby et al. Neurology. 2020;95:e469-e79) assessing erenumab in people with EM. The Committee noted that 80% of the participants completed the extension study. The Committee noted that the reduction in monthly migraine days was -4.6 days.

10.50. The Committee noted the 52-week open label extension of the LIBERTY trial (Goadsby et al. Neurology. 2021;96:e2724-e35) assessing erenumab in people with EM. The Committee noted that 57% of the participants completed the extension study. The Committee noted that the reduction in monthly migraine days was -3.7 days. The Committee considered the absolute reduction of monthly migraine days is

less in EM than in CM, however, the reduction is still clinically meaningful for people with EM. The Committee noted during the study extension that acute medication (triptan) use reduced in people treated with erenumab.

10.51. The Committee noted evidence of patient reported outcomes from an open-label, multicentre 5-year extension to Study 275 of erenumab in EM (Ashina et al. Eur J Neurol. 2021;28:1716-25). The Committee noted that the reduction in monthly migraine days and patient reported outcomes in this study were significant. The Committee noted that a reduction in presenteeism (MIDAS score: -9.7) and absenteeism (MIDAS score: -8.7) in the workplace and home was beneficial, as measured by MIDAS. The Committee noted that the total reduction in MIDAS score was -18.4 (standard deviation: 2.0). The Committee noted that a reduction of MIDAS score of >5 was indicative of a clinically meaningful improvement.

10.52. The Committee noted a 24 week, double blind, randomised trial comparing erenumab and topiramate in people with EM (mean monthly headache days 11.5 days) (Reuter et al. Cephalalgia. 2022;42:108-18). The Committee noted the discontinuation of erenumab (10.6%) was lower than topiramate (38.9%) (odds ratio: 0.19 (95% CI, 0.13-0.27) and relative risk 0.27 (95% CI, 0.20-0.37) *P*<0.001). The Committee noted that fewer people reached the ≥50% reduction from baseline in migraine days per month in the topiramate group (31.2%) compared to the erenumab group (55.4%) (odds ratio: 2.76 (95% CI, 2.06-3.71) and relative risk 1.78 (95% CI, 1.50-2.11) *P*<0.001). The Committee considered erenumab to be more tolerable and effective than topiramate in reducing monthly migraine days.

10.53. The Committee noted the reported results from the ARISE and STRIVE studies assessing functional patient reported outcomes (The Migraine Functional Impact Questionnaire (MFIQ)) with erenumab in people with EM (Kawata et al. Headache. 2022;62:159-68). The Committee noted that MFIQ measured the impact of migraine on four domains (physical function (PF), social function (SF), and emotional function (EF); and usual activities (UA). The Committee noted that in the ARISE study, to month 3, the greater reductions were observed in the physical and emotional domains compared to placebo. The Committee noted that in the STRIVE study, to month 4 to 6, improvements were observed in the physical, emotional, social, and usual activities domains compared to placebo. The Committee considered that there was not a strong indication of a functional difference (as measured from MFIQ) in groups receiving 70 mg or 140 mg of erenumab.

10.54. The Committee noted the following two randomised controlled trials relating to the use of erenumab in EM:

- Lanteri-Minet et al. J Neurol Neurosurg Psychiatry. 2021;92:466-72
- Ferrari et al. J Neurol Neurosurg Psychiatry. 2022;93:254-62

10.55. The Committee noted the following three randomised controlled trials relating to the use of galcanezumab in people with EM:

- Stauffer et al. JAMA Neurol. 2018; 75: 1080-88
- Skljarevski et al. Cephalalgia. 2018;38:1442-54
- Hu et al. J Headache Pain. 2022; 23:90

10.56. The Committee noted again the CONQUER trial open label extension follow up and quality of life data relating to the use of galcanezumab in CM and EM:

- Reuter et al. Adv Ther. 2021;38:5465-83
- Tepper et al. Clin Drug Investig. 2022; 42: 263–75

10.57. The Committee noted the ADVANCE trial of atogepant in people with EM (Ailani et al. N Engl J Med 2021;385:695-706), which included additional reporting on patient reported outcomes (Lipton et al. Neurology. 2023;100:e764-e777).

10.58. The Committee noted the 52 month open label extension study of the ADVANCE trial of atogepant in people with EM (Ashina et al. Headache 2023;63:79-88). The Committee noted the reported mean change in headache days from baseline at 52 weeks was -5.2 days (standard deviation 0.2 days) and 84.2% of people had at least a 50% response (reduction in monthly migraine days). The Committee considered that this indicated that there is continued benefit for use of atogepant in EM.

Cluster headaches

10.59. The Committee noted a phase III, placebo-controlled, randomised control trial in people with chronic cluster headaches using galcanezumab 300 mg (Dodick et al. Cephalalgia. 2020;40:935-48). The Committee noted that this trial reported that galcanezumab was not superior to placebo in reducing mean weekly frequency of cluster headache attacks in people with chronic cluster headaches (P>0.05). The Committee noted that these people were allowed to take other preventative treatments including verapamil (50% of participants), lithium (13%), valproate (6%) and melatonin (3.5%). The Committee considered that the evidence for the effectiveness of galcanezumab in people with chronic cluster headaches using other preventative treatments was poor.

10.60. The Committee noted a phase III, placebo controlled, randomised trial in people with episodic cluster headaches (Goadsby et al. N Engl J Med 2019;381:132-41). The Committee noted that the mean change in weekly frequency of cluster headache attacks across weeks 1 to 3 reported a difference in reduction comparing placebo and galcanezumab (-5.2 v -8.7 (P=0.04)). The Committee noted that this trial did not allow other preventative treatments to be used.

10.61. The Committee noted two additional studies relating to the use of galcanezumab in cluster headaches:

- Lainez et al. Headache. 2022; 62:65–77
- Kudrow et al. Headache. 2020;60:2254-64.

Safety, effects on health systems

10.62. The Committee considered that the adverse effect profile of galcanezumab to be similar to placebo, with the most common reaction being injections site reactions and nasopharyngitis. The Committee noted that the FDA galcanezumab datasheet reports total adverse effects as 27 per 1000 people treated with serious events at 1.3 per 1000 people treated. The Committee considered that there was caution required in people with cardiovascular disease. The Committee noted that trials of galcanezumab in people with CM aged 12-17 years and in people with EM aged 6-17 years are ongoing. The Committee considered that the safety of galcanezumab is not established in pregnancy and breastfeeding.

10.63. The Committee noted that over 2500 people have been treated with erenumab in registration studies. The Committee noted that the adverse effects reported with erenumab were most commonly injection site reactions, constipation, muscle spasms and pruritus and most were mild to moderate in severity.

10.64. The Committee noted that the most common adverse effects with atogepant treatment were constipation, nausea, and decreased appetite. The Committee considered that the safety and tolerability of erenumab, galcanezumab, and atogepant was superior to other currently available preventatives in New Zealand.

10.65. The Committee considered the consequences to health systems in the post-hoc analyses from the REGAIN trial including people with CM only (Tobin et al. J Med Econ. 2022;25:1030-8). The Committee noted the reported medication overuse at baseline was 64% of all participants and at month 3 was 33% in the galcanezumab group and 46% in the placebo group (*P*>0.001). The Committee noted the reported reduction in healthcare visits to emergency departments (58-75% reduction) and healthcare professional visits (54-67% reductions).

10.66. The Committee noted the reported reduction in healthcare visits and medication use in the post-hoc analyses from the CONQUER trial including people with EM and CM (Ambrosini et al. J Manag Care Spec Pharm. 2022;28:645-56). The Committee noted the reported reduction in emergency department visits was higher in the galcanezumab group (22.7 events per 100 patient-years to 7.5 events per 100 patient-years, *P*=0.007) compared to the placebo group (13.1 events per 100 patient-years to 12.6 events per 100 patient-years, *P*=0.930). The Committee considered that meaningful treatment comparisons for migraine-specific hospitalisation could not be made because only two events, both in the placebo group, occurred over the 6-month period.

10.67. The Committee noted that internationally that galcanezumab and erenumab have been assessed in Australia (erenumab July 2018, March 2019; galcanezumab July 2019, March 2022, November 2020), Canada (erenumab July 2020; galcanezumab January 2022), Scotland (erenumab April 2019; galcanezumab March 2021), and England/Wales (erenumab March 2021; galcanezumab November 2020). The Committee noted that erenumab was recommended in Canada, Scotland, and England/Wales but not in Australia for either EM or CM. The Committee noted that galcanezumab was recommended for CM and EM in Australia (>8 headache days a month for EM), Canada, England/Wales and Scotland. The Committee noted that atogepant was being reviewed by NICE (England/Wales) and had not yet been assessed by Australia, Canada or Scotland.

Suitability

10.68. The Committee noted the delivery of erenumab was with a pre-filled pen injector. The Committee noted that erenumab must be stored in the refrigerator but can be kept at room temperature for up to 14 days before administration.

10.69. The Committee noted the delivery of galcanezumab was with a pre-filled pen injector. The Committee noted that galcanezumab must be stored in the refrigerator but can be kept at room temperature for up to 7 days before administration.

10.70. The Committee noted that erenumab and galcanezumab are delivered in similar delivery systems to sumatriptan injections that people with migraine commonly use, and considered them likely to be suitable. The Committee considered that the disposal of injectors at the dispensing pharmacy was not certain and that this could become a burden for secondary care. The Committee considered that monthly dosing may improve adherence compared to daily medicines.

10.71. The Committee noted that atogepant is a once daily oral tablet that does not require training or special storage for people using the medicine. The Committee noted that due to drug interactions with strong CYP3A4 inhibitors and/or strong OATP inhibitors atogepant requires a dose reduction from 60 mg to 10 mg daily.

Cost and savings

10.72. The Committee noted that there was a significant price difference between the treatments considered.

10.73. The Committee considered that in addition to propranolol, other beta blockers such as metoprolol and nadolol could be used for the treatment of CM and EM. The

Committee noted some of the listed comparators (not specified) were not appropriate for women of childbearing potential.

10.74. The Committee noted a European-based cross-sectional web-based survey that reported preventative medications used by self-selected people with migraine (Bloudek et al. J Headache Pain. 2012;13:361-78). The Committee considered that the proportion of people with EM taking a preventative for migraine was estimated as 30%. The Committee considered that the median number of preventatives tried was two for people with migraine in New Zealand with EM. The Committee noted that this survey-based study sourced a select sample (not a random population- based sample) that was not necessarily representative of all people with migraine, and did not differentiate EM by number of migraine days per month.

10.75. The Committee noted the ObserVational survey of the Epidemiology, tReatment and Care of MigrainE (OVERCOME (US)) (Lipton et al. Headache. 2022;62:122-40). The Committee noted that this was a prospective, longitudinal, multicohort, demographically representative web-based survey quota-sampling adults with and without migraine in the United States, surveying experience of headache or migraine disaggregated by monthly migraine or headache days. The Committee considered that this was transferable to the New Zealand context as it is most similar to population-based data.

10.76. The Committee considered that the EM group as described in the Special Authority criteria would be estimated as three times that of the CM group as based on the OVERCOME (US) study. The Committee noted that it was reported that in the EM group 30% would be using a preventative treatment and that the reported use of preventatives in CM was 45%. The Committee considered that it was reasonable to assume that 1.8% of people have CM and that 30% of these people with be taking preventative treatments.

10.77. The Committee considered that the CM prevalence in New Zealand to be 1.8% (12% of all people with migraine), as considered by PTAC and estimated in the OVERCOME (US) study (Lipton et al. 2022). The Committee noted that in the OVERCOME (US) study the median number of preventative treatments tried was three for people with CM. The Committee considered that this would include up to 50% of people with CM.

10.78. The Committee considered that the proportion of CM and EM likely to be unsuitable or intolerant to currently funded treatments included being child-bearing potential (valproate and topiramate not recommended) and beta blocker use associated with hypotension in young women.

10.79. The Committee considered that at three months 30-40% of people with CM and 40-60% of people with EM would be meet the proposed Special Authority criteria for renewal (at least 30% and 50% reductions in monthly migraine days for CM and EM respectively and treatment being tolerated), based on randomised controlled trial evidence considered.

10.80. The Committee considered that medical resource use was best estimated in the REGAIN (Tobin et al. J Med Econ. 2022;25:1030-8) and CONQUER (Ambrosini et al. J Manag Care Spec Pharm. 2022;28:645-56) open label extension analyses.

Funding criteria

10.81. The Committee noted the Special Authority criteria proposed for CM and EM were as recommended by PTAC for erenumab for CM in August 2021.

10.82. The Committee considered it reasonable to reduce the reduction of migraine days' outcome metric for people with CM to become a ≥30% reduction within 3 months, as the evidence and guidance indicated that the reduction in migraine frequency in CM

may still be clinically meaningful at rates lower than the ≥50% reduction considered necessary for clinical meaning for EM. The Committee also considered that the health need of those of CM is greater than people with EM, and thus capacity to benefit would be greater in CM than EM for any given rate of reduction, reinforcing the lowering of reduction thresholds needed for clinically meaningful effects in CM. The Committee considered the renewal after 3 months' requirement aligned with the placebo-controlled trial evidence, given there was a large placebo effect in trials and the evidence from the unblinded non-randomised open label extensions beyond 3 months could not reliably or validly differentiate treatment from placebo effects.

10.83. The Committee considered that, for the trialling of other medicines for migraine, that as many options available should be trialled, with up to three agents before initiating CGRP antagonists.

Summary for assessment

10.84. The Advisory Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for erenumab, galcanezumab, and atogepant if they were to be funded in New Zealand for **chronic migraine**. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals with chronic migraine, defined as experiencing at least 15 headache days per month (with at least eight days having headache with migraine features), for at least three months; and either refractory to at least three funded prophylactic agents or funded prophylactic treatments are clinically unsuitable or not tolerated.
Intervention	• erenumab given via subcutaneous injection once every four weeks at a dose of 70 mg. some individuals may benefit from the 140 mg dose once every four weeks • galcanezumab loading dose of 240 mg subcutaneous injection, followed by monthly 120 mg subcutaneous injections • atogepant 60 mg tablet once daily (for those on concomitant strong CYP3A4 inhibitor and/or strong OATP inhibitors 10 mg dose) Treatment continuation at 12 weeks if patient has had a **>30%** reduction in headache days per month.
Comparator(s) (NZ context)	Current 4th line treatment with recommended available prophylactic agents. • propranolol or other beta-blocker (eg metoprolol or nadolol) • amitriptyline • topiramate • pizotifen sodium valproate (not for those of child-bearing potential)
Outcome(s)	**Primary outcomes** Reduction in the mean number of headache/migraine days per month (>30% reduction) (REGAIN trial, 2018) Reduced days per month requiring acute migraine medication. **Health-related quality of life outcomes** Improvements in MSQv2 score, MIDAS EQ-5D

Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.

10.85. The Advisory Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for erenumab, galcanezumab, and atogepant if they were to be funded in New Zealand for **episodic migraine**. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals with episodic migraine, defined as experiencing at least 4 headache days per month and less than 15 headache days, for at least 3 months and either refractory to at least three funded prophylactic agents or prophylactic agents are clinically unsuitable or not tolerated.
Intervention	• erenumab given via subcutaneous injection once every four weeks at a dose of 70 mg. some individuals may benefit from the 140 mg dose once every four weeks • galcanezumab loading dose of 240 mg subcutaneous injection, followed by monthly 120 mg subcutaneous injections • atogepant 60 mg tablet once daily (for those on concomitant strong CYP3A4 inhibitor and/or strong OATP inhibitors 10 mg dose) Treatment continuation at 12 weeks if patient has had a >**50%** reduction in headache days per month.
Comparator(s)	Current 4th line treatment with recommended available prophylactic agents. • propranolol • amitriptyline • topiramate • pizotifen • sodium valproate (not for those of childbearing potential)
Outcome(s)	**Primary outcomes** Reduction in the mean number of headache/migraine days per month (>50% reduction) (ADVANCE trial, 2021) Reduced days per month requiring acute migraine mediation. **Health-related quality of life** Improvements in MSQ-RFR v2.1
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

11. Siponimod - treatment of patients with secondary progressive multiple sclerosis (SPMS)

Application

11.1. The Committee noted that Pharmac staff sought specific advice regarding potential funding criteria for siponimod (Mayzent), an oral tablet for the treatment of secondary

progressive multiple sclerosis (SPMS). This advice was sought following PTAC's August 2022 review of:

- An application from Novartis New Zealand Limited for siponimod for the treatment of active SPMS
- A submission in support of the funding of siponimod provided by Multiple Sclerosis New Zealand (MSNZ), which included consumer stories.

11.2. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

11.3. The Committee **recommended** that siponimod be funded for the treatment of active SPMS with a **medium priority**, within the context of neurology treatments, subject to the following Special Authority criteria:

> **Initial application — Secondary Progressive Multiple sclerosis**
> Applications only from a neurologist or general physician. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. Diagnosis of secondary progressive multiple sclerosis confirmed by a neurologist; and
> 2. Person has an EDSS score between 3.0–6.5; and
> 3. Person has a history of relapsing remitting multiple sclerosis; and
> 4. Person has documented EDSS progression in the past two years.
>
> Note: Treatment on two or more funded multiple sclerosis treatments simultaneously is not permitted.
>
> **Renewal — Secondary Progressive Multiple sclerosis**
> Applications only from a neurologist or general physician. Approvals valid for 12 months for applications meeting the following criteria:
> 1. Person has had an EDSS score of 3.0 to 6.5 (inclusive) at any time in the last six months (ie the person has walked 20 metres or more with or without two aids without rest in the last six months).
>
> Note: Treatment on two or more funded multiple sclerosis treatments simultaneously is not permitted.

11.4. In making this recommendation, the Committee considered:

11.4.1. The high health need and impact on health-related quality of life for those with SPMS and their family/whānau, and wider society, it being very high need for the individual due to progressive disability.

11.4.2. The absence of effective funded treatments specifically for SPMS.

11.4.3. The good quality, if poor strength, evidence reporting a modest, but real and impactful health benefit of siponimod in slowing the progressive disability of SPMS, which would also convey benefits to family, whānau, and wider society.

11.4.4. The heath sector and pharmaceutical savings that would be expected from siponimod replacing infused MS treatments.

Discussion

11.5. PTAC and PTAC Advisory Committees may differ in the advice they provide to Pharmac, including recommendations priority, due to the Committees' different, albeit complementary, roles, expertise, experience, and perspectives.

Māori impact

11.6. The Committee discussed the impact of funding siponimod for the treatment of SPMS on Pharmac's Hauora Arotahi (Māori health areas of focus) and Māori health outcomes.

11.7. The Committee noted that MS is not considered to be part of the Hauora Arotahi.

11.8. The Committee noted that there is a lower prevalence of overall MS in Māori compared to non-Māori and noted the paucity of data reporting on the severity and subtypes of MS in Māori (including SPMS). The Committee considered however that Māori in general experience greater barriers to accessing health services, which may result in potentially worse MS health outcomes compared to non-Māori, and therefore considered that funding siponimod may be advantageous to Māori with SPMS.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system

11.9. The Committee discussed the impact of funding siponimod on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee was not aware of any groups experiencing health inequities disproportionately affected by SPMS.

Background

11.10. The Committee noted that in August 2022, PTAC reviewed the Novartis application and MSNZ submission and recommended that siponimod for the treatment of active SPMS be listed with a low priority, subject to Special Authority criteria. In making this recommendation, PTAC considered the severe unmet health need and impact on health-related quality of life for those with SPMS and their family/whānau, noting there are currently no funded treatments for SPMS; and the good quality, poor strength evidence that demonstrated the health benefit of siponimod in the treatment of SPMS.

11.11. The Committee noted that PTAC also recommended Pharmac seek further advice from the Neurological Advisory Committee regarding appropriate Special Authority criteria for siponimod for SPMS.

Health need

11.12. The Committee considered that people with SPMS have a very high health need due to becoming disabled and the impact this has on their ability to perform daily tasks and work. The Committee noted that need is based on disability rather than disease progression with or without relapse, and that the Expanded Disability Status Scale (EDSS) reflects ambulation and other impacts.

11.13. The Committee noted that about 4130 people have MS in New Zealand, of which 85% of have relapsing onset disease and 15% have primary progressive MS (PPMS), with higher proportions of people with progressive MS at higher disability scores (New Zealand Institute of Economic Research. 2020). The Committee noted that there are eight currently funded MS treatments, with a range of formulations funded for people with relapsing onset MS with EDSS score of 0 to 6.0 with new MRI and relapse activity in the two years prior. The Committee noted that ocrelizumab will be funded from 1 October 2023 for people with PPMS with EDSS score of 2.0 to 6.5.

11.14. The Committee noted that most clinical trials investigating the treatment of MS did not include people with SPMS. The Committee considered that about half of people with SPMS are likely to be currently receiving funded RRMS treatments, with the other half not being able to access them due to having higher EDSS scores. The Committee considered that people with SPMS with an EDSS score of less than 6.5 (ie EDSS 0 to 6.0 inclusive) would still be able to access and receive benefit from funded RRMS treatments; in particular, the Committee considered that most with EDSS scores of 4-5 would currently be on treatment.

11.15. The Committee noted that the application proposed siponimod be targeted to those with EDSS 3.0 to 6.5, and considered that this group was quite similar to the population who will be eligible to receive funded ocrelizumab, however, siponimod access was proposed to have no requirements to have recent relapse or MRI activity. The Committee considered that there were two population groups to consider for this application:

11.15.1. Group 1 - Those who have met criteria for relapsing MS disease-modifying treatments and have not met stopping criteria due to EDSS score of 6.0 or less. The Committee considered that this group would receive currently funded RRMS treatments. The Committee considered that this group is estimated to be made up of approximately 250 people over five years, based on the following assumptions:

- Approximately 2100 people are currently receiving disease-modifying treatments (Pharmac dispensing data), 1050 of whom are likely to be at EDSS 3.0-6.0
- 25% of these people would be likely to switch to siponimod if it were funded.

11.15.2. Group 2 – Those who are not on disease-modifying therapy and do not meet RRMS-based funding criteria either from having no recent relapse and MRI activity or because of EDSS score of ≥6.5. The Committee considered that this group would currently receive best supportive care and estimated that approximately 450 people with MS would be in this group, based on the following assumptions:

- 2000 of the ~4000 people with MS in New Zealand are likely to be EDSS 3.0-6.5, and 1650 of this group are likely to have relapsing-remitting MS
- 300 people are likely to have already progressed to EDSS 6.5, 150 of whom may have progressed in the last two years and therefore be eligible to receive siponimod if funded (as per the proposed eligibility criteria)
- Approximately 300 of the remaining people with EDSS 3.0-6.0 would not currently be receiving MS treatments, and may receive siponimod if funded (as per the proposed eligibility criteria).

11.16. The Committee considered that there is robust New Zealand evidence that MS is less prevalent in Māori than in than Europeans and is also less prevalent in Pacific peoples than in NZ Europeans. However, the Committee noted that there is no data for the severity of MS in Māori and considered that barriers to healthcare access may result in later diagnosis in Māori and consequently, that Māori are likely to receive less benefit from treatment due to having higher EDSS scores at the time of treatment commencement. The Committee also noted that Māori have higher rates of elevated BMI and smoking than NZ Europeans, both of which are associated with worsening MS symptoms and disease progression (Manatū Hauora, Ministry of Health. 2021). The Committee acknowledged the substantial impact of MS on whānau in addition to the impact on the individual.

Health benefit

11.17. The Committee noted that siponimod is a selective sphingosine-1-phosphate (S1P) receptor modulator in a similar class as fingolimod, which is funded for relapsing MS. The Committee noted that siponimod is taken orally with an initial dose of 0.25 mg titrated up to 2 mg maintenance. The Committee noted that, like fingolimod, siponimod acts as an immunomodulator that crosses the blood-brain barrier and is thought to have effects on glial cells, which is of particular relevance to the treatment

of progressive MS. Members noted that siponimod is more receptor-specific and has a lower incidence of first dose bradycardia compared with fingolimod, and that observation in hospital with the first dose of siponimod is only required for individuals with a history of cardiac issues.

11.18. The Committee noted that the evidence for siponimod for SPMS comes from the phase III EXPAND trial, a randomised, double-blind, placebo-controlled study of median 21.3 months duration that investigated the efficacy and safety of siponimod in patients with SPMS (Kappos et al. Lancet. 2018;391:1263-73; Benedict et al. Neurology. 2021;19:e376-86). The Committee noted that EXPAND participants were randomised (2:1) to once-daily oral siponimod 2 mg or placebo and that key eligibility criteria included all of age 18-60 years, a diagnosis of SPMS, EDSS score of 3.0-6.5 at screening (median 6.0), a history of RRMS, documented EDSS score progression in the past 2 years, and no evidence of relapse in the previous 3 months.

11.18.1. The Committee noted that the primary endpoint of EXPAND was time to 3-month confirmed disability progression (3mCDP) defined as a 1-point increase in EDSS if the baseline score was 3.0-5.0, or a 0.5-point increase if the baseline score was 5.5-6.5. The Committee noted that 288/1096 (26%) who received siponimod had 3mCDP and 173/545 (32%) who received placebo had 3mCDP (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.65 to 0.95; relative risk reduction 21%; *P*=0.013). The Committee noted that this absolute difference of 6% was a small but proven benefit and considered it would be real and meaningful in the context of SPMS disability progression.

11.18.2. The Committee noted that the hazard ratios of some EXPAND subgroup analyses may not have been statistically significant due to confidence intervals crossing one, but with the caveat that individuals with lesions at baseline experienced more point estimate treatment effect from siponimod, and that younger people might also experience a higher treatment effect compared with older people.

11.18.3. The Committee noted that 21% of participants had gadolinium positive lesions on MRI (Gad+) at baseline; that 64% of participants had no relapses in the two years before the trial (of these, 18% had Gad+ lesions); and that 52% of participants had neither relapse nor Gad+ in the two years before the trial. The Committee noted that 14.9% of the placebo group with no relapses in the two years prior to study had relapses during the trial (Cree et al Mult Scler. 2021;27:1564-76). The Committee noted that 33% of the placebo group compared with 11% of the siponimod group developed Gad+ lesions during the trial. The Committee considered that this suggests patients without Gad+ or relapse activity at baseline would become active subsequently over a couple of years, which it considered was relevant and important, and noted that some other jurisdictions limit funded access to siponimod to just those with Gad+ on MRI with a requirement for annual MRI.

11.18.4. The Committee noted observational data from a patient population with similar EDSS distribution to those in the EXPAND clinical trial and considered the authors generalised the HR from EXPAND to their population (Regner-Nelke at al. Neurol Res Pract. 2022;4:55).

11.18.5. The Committee noted a post hoc analysis of participants with active SPMS (aSPMS), defined as having relapses in the two years prior to the study and/or Gad+ lesions at baseline, who received oral siponimod (2 mg/day) or placebo for up to three years in EXPAND (Gold et al. J Neurol. 2022;269:5093-104). The Committee noted that, of the 1645 EXPAND participants, 779 (47.4%) who received at least one dose of study drug had aSPMS according to the definition and 621 (79.7%) of those completed the

study. The Committee noted that the reduction in risk of 3mCDP with siponimod vs placebo was greater in people with aSPMS (HR: 0.69; 95% CI: 0.53 to 0.91; *P*=0.0094) than the whole trial population (HR 0.79, as reported above).

11.18.6. The Committee noted evidence of improved outcomes for Symbol Digit Modalities Test (SDMT) in people with active SPMS (not significant for inactive) in EXPAND (Penner et al. Virtual: Presented at MSVirtual2020, 8th Joint ACTRIMS-ECTRIMS Meeting; 2020 September 11-13; P0806).

11.18.7. The Committee noted a post-hoc analysis of the same subgroup of EXPAND participants with active SPMS (*n*=779) as that performed by Gold et al., in which data were analysed for subgroups stratified by age at baseline (primary cut-off: < 45 year ≥ 45 years; and secondary cut-off: < 50 years or ≥ 50 years) and by disease duration (DD) at baseline (< 16 years or ≥ 16 years) (Hua et al. Mult Scler Relat Disord. 2023;75:104766). The Committee considered that the effects of siponimod were similar using the different disease durations, but that the evidence suggests that more benefit is received from siponimod in younger patients.

11.18.8. The Committee noted that an analysis reporting the associations between siponimod or placebo with total brain volume (secondary objective), cGM and thalamic volume, and nMTR (exploratory objectives) in EXPAND provided some evidence of slowing the progression of MRI markers of degeneration (Arnold et al. Mult Scler. 2022;28:1526-40). The Committee considered this outcome has been validated as being relevant for people with MS.

11.19. The Committee considered that the reduction in the speed of confirmed disability progression, as measured by EDSS scores, led to EDSS-associated health-related quality of life improvements and lower mortality risk. The Committee considered that the evidence indicated there are real and meaningful, although modest, benefits from siponimod in slowing the disability from MS. The Committee considered that siponimod would convey some benefits to family, whānau, and wider society from this slowed progression of disability.

11.20. The Committee noted that there were slight differences in efficacy between the groups with SPMS, with better evidence for slowing disability progression in those patients who are similar to the EXPAND trial population and lower efficacy (but still effective) in those with EDSS score of 6.5 who were likely to be similar to the overall EXPAND population (median EDSS 6.0), based on post-hoc analyses.

Suitability

11.21. The Committee considered that the oral formulation of siponimod is very convenient and that it would replace some MS treatment infusions where people switch from IV treatment.

Cost and savings

11.22. The Committee considered that the clinical decision to switch an individual with SPMS from a current infused MS treatment to siponimod, if funded, would depend on the person's comorbidities and risk of infection among other factors. The Committee considered that there would be savings to the pharmaceutical budget and health sector resulting from any switches from infusion treatments to siponimod. The Committee further considered that there would be savings as a result of slowing MS progression additional to any savings from switching (ie switching to a lower cost medicine especially if the individual has a higher EDSS score and is then using a more effective drug for progressive MS).

11.23. The Committee considered that, if funded, a group of people with SPMS would require neurologist appointments to consider initiation of siponimod treatment and that this might displace other people on neurology waitlists, given these clinics are currently over capacity. The Committee considered that people commencing treatment with siponimod would need to have an annual assessment in clinic or by phone with a specialist, and that this would not be feasible to instead manage in primary care.

11.24. The Committee considered that people receiving siponimod would require blood tests for on-treatment monitoring including hepatitis B antigen testing.

Funding criteria

11.25. The Committee considered that the funding criteria as proposed, including renewal, were appropriate to ensure people who would benefit most would not be excluded from accessing siponimod, and that outcome measures such as EDSS score and walking test were used appropriately.

11.25.1. The Committee noted that some other jurisdictions require MRI or Gad+ activity and a specific type of walk test, however, these were not considered necessary or appropriate to include in the New Zealand setting.

11.25.2. The Committee considered that specifying an ophthalmologist assessment of optical coherence tomography (OCT) was also not necessary for funding criteria, although some people might require this monitoring while on siponimod, noting it is performed for people receiving fingolimod after about three to six months on treatment.

Summary for assessment

11.26. The Committee considered that Pharmac might reasonably use data from the treatment of secondary progressive or primary progressive MS for comparator efficacy in its assessment of siponimod, given that the EXPAND trial comparator was placebo.

11.27. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for siponimod if it were to be funded in New Zealand for SPMS. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

	Group 1	Group 2
Population	People with SPMS with an EDSS score of 3.0-6.0, a history of RRMS and documented EDSS progression in the past two years (ie actively progressing disease). This population group is comprised of those who have met criteria for relapsing MS disease-modifying treatments and have not met stopping criteria, as their EDSS is 6.0 or less.	People with SPMS with an EDSS score of 3.0-6.5, a history of RRMS and documented EDSS progression in the past two years (ie actively progressing disease). This population group is comprised of those who are not on disease-modifying therapy and do not meet criteria because of no recent relapse and MRI activity or because their EDSS is 6.5.
Intervention	Daily 2 mg siponimod or 1 mg for those with the CYP2C9*2*3 or 1*3	As per Group 1

	genotype (following titration period) taken orally until disease progression past EDSS 6.5. It is estimated that <10% of people would receive the lower dose. (CYP2C9*2*3 or 1*3 genotypes in 5.5% of Māori and Pacific peoples based on Roberts et al. Joint Bone Spine. 2014;81:160-3).	
Comparator(s)	Currently funded RRMS treatments – with no positive trials in SPMS, currently funded treatments would be assumed to not slow disease progression.	Best supportive care
Outcome(s)	Slowing of confirmed disability progression as measured by EDSS, leading to EDSS-associated health-related quality of life improvements and lower mortality risk. 3mCDP HR 0.79 from the EXPAND trial overall population	Slowing of confirmed disability progression as measured by EDSS, leading to EDSS-associated health-related quality of life improvements and lower mortality risk • using the 3mCDP HR of 0.79 from EXPAND trial overall population for those at EDSS 6.5 using the 3mCDP HR of 0.87 from the EXPAND trial (among those with no relapses in the last two years) for those with inactive disease
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.		