

Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 18 August & 19 August 2022

This meeting was held via Zoom

Objective advice to PHARMAC

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1. Present:

PTAC members:

Jane Thomas (Chair)
Marius Rademaker (Deputy Chair)
Alan Fraser
Brian Anderson
Bruce King
Elizabeth Dennett
Giles Newton Howes
Jennifer Martin
Lisa Stamp
Matthew Strother
Rhiannon Braund
Robyn Manuel
Simon Wynn Thomas
Stephen Munn
Tim Stokes

Apologies:

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2. Summary of recommendations

2.1. The following recommendation summary is in order of the discussions held at the meeting.

Pharmaceutical and Indication	Recommendation
Paracetamol 1000 mg with ibuprofen 300 mg in 100 ml solution for infusion be funded in hospital for the treatment of acute pain if cost-neutral to the combination of IV paracetamol and IV parecoxib when used in the same indication (including relevant health system costs).	Cost-neutral
Ticagrelor for the prevention of atherothrombotic events in patients with minor stroke or high-risk transient ischaemic attack	Low Priority
Siponimod for the treatment of active SPMS	Low Priority
Epidyolex brand of cannabidiol oral liquid for the treatment of Dravet Syndrome	High Priority
Daily Essential Nutrients for the treatment of attention deficit and hyperactivity disorder (ADHD)	Low Priority
Fomepizole for methanol poisoning	High Priority

3. The role of PTAC, Specialist Advisory Committees and meeting records

3.1. This meeting record of PTAC is published in accordance with the Pharmacology and Therapeutics Advisory Committee (PTAC) [Terms of Reference 2021](#), and Specialist Advisory Committees [Terms of Reference 2021](#).

- 3.2. The PTAC Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC and Specialist Advisory Committees.
- 3.3. Conflicts of Interest are described and managed in accordance with sections 6.4 of both the PTAC Terms of Reference and Specialist Advisory Committee Terms of Reference.
- 3.4. PTAC and Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. PTAC may therefore, at times, make recommendations that differ from Specialist Advisory Committees', including the priority assigned to recommendations, when considering the same evidence. Likewise, Specialist Advisory Committees may, at times, make recommendations that differ from PTAC's, or from other Specialist Advisory Committees', when considering the same evidence.

Pharmac considers the recommendations provided by both PTAC and Specialist Advisory Committees when assessing applications.

4. Record of PTAC meeting held 19 May & 20 May 2022

- 4.1. The Committee reviewed the record of the PTAC meeting held on 19 May & 20 May 2022
- 4.2. The Committee Accepted the record.

5. Specialist Advisory Committee Record

Analgesics Specialist Advisory Committee

- 5.1. The Committee (PTAC) reviewed the record of the Analgesic Advisory Committee held on 5 May 2022. PTAC noted the recommendations made by the Committee:
 - that ketamine be listed in Section B of the Pharmaceutical Schedule for the treatment of palliative care patients in the community with intractable pain not adequately controlled with opioids with a high priority within the context of analgesic, anti-emetic and anaesthetic treatments, subject to endorsement [detailed in the [full record](#)].
 - that lidocaine 10% be listed in Section B and Section H of the Pharmaceutical Schedule for the treatment of terminally ill patients whose (mainly neuropathic) pain is not controlled, and the IV route is not appropriate with a high priority, within the context of analgesic, anti-emetic, and anaesthetic treatments, subject to endorsement [detailed in the [full record](#)].
 - that subcutaneous (SC) levetiracetam (inj 100 mg per ml, 5 ml vial) be listed in Section B of the Pharmaceutical Schedule with a medium priority, within the context of analgesic, anti-emetic and anaesthetic treatments, subject to endorsement [detailed in the [full record](#)].
 - that methylnaltrexone bromide for opioid induced constipation be listed with a medium priority within the context of analgesic, antiemetic and anaesthetic treatments subject to Special Authority criteria [detailed in the [full record](#)].
- 5.2. Regarding item 10, Ketamine (community use) – Pain – palliative care patients with intractable pain not controlled with opioids:
 - The Committee noted the Analgesic Advisory Committee had recommended ketamine be funded for the treatment of palliative care patients in the community with intractable pain not adequately controlled with opioids with a high priority.
 - The Committee considered that currently hospitals can use ketamine for any indication, including palliative care, and therefore there could be inequities in primary care.

- The Committee considered that the experts on the Specialist Advisory Committee had on the ground experience with palliative care and acknowledged the high health need of palliative care patients and their whānau.
- The Committee considered that there was a risk of ketamine misuse in the community setting and caution would be needed with regards to access criteria.
- The Committee considered some level 4 evidence (eg case reports or case series) and/or real-world data would be useful to assist with interpreting the benefit from ketamine in the palliative care setting.
- The Committee considered a randomised, double-blind, placebo-controlled trial by Hardy et al. (Hardy et al. [J Clin Oncol. 2012;30:3611-7](#)) that reported no benefit of ketamine over placebo. The Committee highlighted concerns that ketamine may do more harm than benefit in the palliative care setting due to psychomimetic adverse effects and that evidence to support positive health outcomes from treatment from ketamine was overshadowed by the adverse effect profile of the drug. The Committee recommended that a paper be bought back for PTAC to review the evidence in full.

5.3. With regard to item 13, methylnaltrexone bromide for the treatment of opioid-induced constipation:

- The Committee noted the Analgesic Advisory Committee had recommended that methylnaltrexone bromide (a peripherally acting mu-opioid receptor antagonist (PAMORA)) for the treatment of opioid-induced constipation be funded with a medium priority.
- Members noted that internationally there are oral PAMORA products (including methylnaltrexone) available and considered that these may be of interest to Pharmac.
- The Committee considered that use in the non-palliative care setting would likely be larger than estimated, and that the assumptions used to inform the patient numbers needed reviewing.
- The Committee recommended that the funding application be bought back to PTAC for its view.
- The Committee considered that it may also be beneficial to seek advice from the Gastroenterology Subcommittee.

Immunisation

5.4. The Committee (PTAC) reviewed the record of the Immunisation Advisory Committee meeting held on 1 April 2022. The Committee noted and agreed with the recommendations, further noting that the recommendations were based on local data and the international literature.

Ad-hoc Covid Treatments Advisory Group Record

5.5. The Committee (PTAC) reviewed the records of the Ad-hoc Covid Treatments Advisory Group meeting held in December 2021. The Committee noted the recommendations and considerations of the Advisory Group and raised no concerns or additional comments regarding these.

Cancer Treatments Advisory Committee

5.6. The Committee (PTAC) reviewed the record of the Cancer Treatments Advisory Committee meeting held on 8 April 2022. The Committee noted the recommendations and considerations of the Advisory Committee and raised no concerns or additional comments regarding these.

6. Correspondence & Matters Arising

Paracetamol 1000 mg with ibuprofen 300 mg in 100 ml solution for infusion (Maxigesic IV) for the treatment of acute pain

Recommendation

- 6.1. The Committee **recommended** that paracetamol 1000 mg with ibuprofen 300 mg in 100 ml solution for infusion be funded in hospital for the treatment of acute pain if **cost-neutral** to the combination of IV paracetamol and IV parecoxib when used in the same indication (including relevant health system costs).

Discussion

Māori impact

- 6.2. The Committee noted that although information had been provided on an unmet health need for Māori with chronic pain, no evidence had been provided linking the incidence of poorly managed acute pain and Māori health outcomes.

Background

- 6.3. The Committee considered correspondence submitted from the Supplier (AFT Pharmaceuticals) of paracetamol 1000mg with ibuprofen 300 mg in 100 ml solution for infusion (Maxigesic IV).
- 6.4. The Committee noted it had previously considered a clinician application for this product at its meeting in May 2022 and had recommended it be declined based on the following:
- The evidence presented displayed that Maxigesic IV provided superior analgesia compared to monotherapy IV paracetamol or IV ibuprofen treatment, however that there was insufficient evidence to demonstrate a synergistic as opposed to an additive effect.
 - The lack of evidence to show that Maxigesic IV would provide a significant health benefit over currently funded treatments or reduce the potential for opioid misuse in the acute pain setting.
 - The potentially subtherapeutic dose of 300 mg ibuprofen in the Maxigesic IV product and the subsequent risk of treatment failure.
- 6.5. The Committee noted it had requested advice from the Analgesics Advisory Committee regarding interpretation of evidence, specifically regarding the health benefit of Maxigesic IV compared to currently funded treatments
- 6.6. The Committee noted the Analgesic Advisory Committee at its May 2022 meeting had noted and agreed with the PTAC recommendation to decline the application for paracetamol 1000mg with ibuprofen 300 mg in 100 ml solution for infusion (Maxigesic IV) and had no additional comments.

Discussion

- 6.7. The Committee noted the information provided from the Supplier sought to address the concerns that PTAC had raised.
- 6.8. The Committee considered that, based on the results reported by Daniels et al ([Daniels et al. Clin Ther. 2019;10:1982-1995](#)), a dose of 300 mg of ibuprofen is likely to have therapeutic value and that some patients would have response at this dose.
- 6.9. The Committee considered that, although no evidence had been provided to demonstrate that 300 mg gave the same benefit as 400 mg, it is documented from pre-clinical studies

that the combination of paracetamol and NSAIDs are likely to be more effective than either agent alone and that the combination is thereby additive.

- 6.10. The Committee considered that no direct evidence had been provided to support reduced use of opiate analgesics in the acute pain setting from use of Maxigesic IV compared to IV paracetamol and IV parecoxib. Furthermore, no evidence was provided to support a reduction in the risk of long-term opioid dependence or misuse.
- 6.11. The Committee noted that, in practice, paracetamol and ibuprofen are routinely given orally for acute pain and IV paracetamol and IV parecoxib are used for those who cannot take oral agents.
- 6.12. The Committee considered that no evidence had been provided to show an additional health benefit from the use of Maxigesic IV compared with IV paracetamol and IV parecoxib, and therefore considered Maxigesic IV should only be funded provided it was no more expensive to the health system than the funded alternatives (IV paracetamol and IV parecoxib).

Erenumab

Application

- 6.13. The Committee reviewed correspondence from the Migraine Foundation Aotearoa New Zealand and the New Zealand Pain Society regarding the funding application for erenumab.
- 6.14. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

- 6.15. The Committee did not consider its previous recommendation, including priority and patient populations for funding, for erenumab should be updated at this time.
- 6.16. The Committee **recommended** that Pharmac seek advice from the Neurological Advisory Committee, specifically regarding the use of erenumab for acute/episodic migraine, as well as chronic migraine, and the treatment paradigm for migraine, should erenumab be funded.

Discussion

- 6.17. The Committee noted that in August 2021 it considered a funding application from a consumer for erenumab (Aimovig) for prophylactic treatment of migraine. At that time, the Committee recommended that erenumab for the treatment of chronic migraine be funded with a low priority, subject to Special Authority criteria ([PTAC record 2021](#)). The Committee did not make a formal recommendation regarding the funding of erenumab for acute/episodic migraine as part of its consideration.
- 6.18. The Committee noted that correspondence from the Migraine Foundation included feedback on specific elements of the August 2021 PTAC record.
- 6.19. The Committee clarified the following prevalence data were accurate and should be used in the evaluation of this funding proposal, acknowledging that these data are a correction of those stated in the August 2021 record.
 - 6.19.1. The estimated prevalence of chronic migraine in New Zealand is 1.8%.
 - 6.19.2. The prevalence of migraine (not including tension-type headache) in New Zealand in 2016 was 15.5%; and

- 6.19.3. The 2006/07 New Zealand Health Survey's migraine prevalence rates were approximately 13% for women and 5.5% for men, where rates were similar for Māori but lower for Pacific and Asian people ([Ministry of Health. 2008](#)).
- 6.20. The Committee noted the correspondence had raised concern regarding the lack of a funding recommendation for acute/episodic migraine. The Committee noted that its reasoning for its lack of a specific recommendation for this group in 2021 had at the time been that patients with chronic migraine would have a greater health need and may receive greater benefit from funded access to erenumab compared with episodic migraine. Members acknowledged that there is evidence for use of erenumab in the episodic setting, however as no further information has become available, at this point of time did not wish to make a formal recommendation for erenumab for acute/episodic migraine. The Committee recommended that Pharmac seek advice from the Neurological Advisory Committee regarding a funding recommendation for both chronic and acute migraine indications.
- 6.21. Members clarified their views regarding the impact on primary care should erenumab be funded. Members noted that currently, the role of primary care in the initiation of biologics is variable and not widely adopted/normalised. Members considered that if erenumab were funded, it is likely that patients would be referred to secondary care services, at least initially (although acknowledged that currently access to secondary care for migraine is limited). The Committee clarified that its advice was not that this could not occur, merely an observation that with current practice it would be unlikely. The Committee considered that in the future, primary care initiation of patients on biologics would likely increase and that improved integration of primary and secondary care would likely strengthen this possibility. The Committee considered that this consideration should not hinder the potential funding of erenumab.

7. Ticagrelor for the prevention of atherothrombotic events in patients with minor stroke or high-risk transient ischaemic attack

Application

- 7.1. The Committee reviewed the application for ticagrelor for the prevention of atherothrombotic events in patients with minor stroke or high-risk transient ischaemic attack.
- 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 ticagrelor for the prevention of atherothrombotic events in patients with minor stroke or high-risk transient ischaemic attack be listed with a **low priority** subject to the following Special Authority criteria:
- Initial application** — (prevention of atherothrombotic events in patients with minor stroke or high risk transient ischemic attack) from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
1. Patient has been diagnosed with minor stroke (NIHSS score 3 or less) or high-risk transient ischemic attack (ABCD2 score 4 or more); and
 2. Ticagrelor will be prescribed for a maximum of 21 days post minor stroke or TIA
- 7.4. In making this recommendation the Committee considered the lack of funded alternative treatment options for patients who are intermediate or poor metabolisers of CYP2C19 for whom clopidogrel does not achieve the desired efficacy, the health need associated with minor stroke and high-risk transient ischaemic attack, the disproportionately high burden of stroke in the Māori population, evidence that supports a higher prevalence of poor or intermediate CYP2C19 status among Māori and Pacific people, and the likelihood that high risk populations would benefit from having access to ticagrelor.

Discussion

Māori impact

- 7.5. The Committee noted that Māori people are significantly more likely to experience stroke during their working lives – up to 15 years younger than New Zealand Europeans, resulting in a disproportionate social and economic burden from premature mortality and disability. The Committee noted that nearly 60 percent of strokes in Māori people occur between age 15 and 65, compared with only 20 percent of strokes in people of European and other ethnicities ([NZIER Research Report 2020](#)). The Committee noted that according to the Ministry of Health (2016), Māori have up to 1.5 times the non-Māori stroke mortality rate and preliminary Ministry of Health data from 2019 reports a similar ratio.
- 7.6. The Committee noted that a 2008 study by Lea et al. reported that the allele frequency for CYP2C19*2 variant, the most common loss-of-function variant for that gene, was 24% for Māori, versus 15% for a matched “Caucasian” population ([N Z Med J. 2008;121:33-7](#)). The Committee were also made aware of a 2015 study which reported that loss-of-function CYP2C19*2 allele was found in 47% of Māori and Pacific study participants, compared to 26% for Caucasians ([Larsen et al. Intern Med J. 2015;45:537-45](#)). The Committee noted that the presence of the CYP2C19*2 alleles only explained 3-4% of on-treatment platelet reactivity.
- 7.7. The Committee noted that testing to determine clopidogrel metabolism status is not readily available in all centres and, further, that a rapid point-of-care test is not currently available in New Zealand. The Committee considered that requiring testing to determine treatment with ticagrelor, which may be more effective for Māori, would contribute to inequitable outcomes by creating a barrier to treatment which may be more beneficial for this patient population.

Health need

- 7.8. The Committee noted that minor stroke (a sudden interruption of blood flow to part of the brain) is generally defined as having a National Institute of Health Stroke Scale (NIHSS) score of 5 or less, though some limit this to a score of 3 or less. The Committee also noted that transient ischemic event (TIA) is a temporary period of symptoms similar to those of a stroke and may only last up to a few hours. The Committee noted that the ABCD2 score is a risk assessment tool designed to improve the prediction of short-term stroke risk after a TIA and that those with TIA considered to be at a high risk of stroke will have an ABCD2 score of 4 or higher. The Committee noted that the highest risk of stroke for those who experienced a TIA is within the first 24 to 48 hours.
- 7.9. The Committee noted that Māori and Pacific people are significantly more likely to experience stroke during their working lives – up to 15 years younger than New Zealand Europeans, resulting in a disproportionate social and economic burden from premature mortality and disability. The Committee noted that nearly 60 percent of strokes in Māori occur between age 15 and 65, compared with only 20 percent of strokes in people of European and other ethnicities ([NZIER Research Report 2020](#)).
- 7.10. The Committee noted that according to the Ministry of Health (2016), Māori have up to 1.5 times the non-Māori stroke mortality rate and preliminary Ministry of Health data from 2019 reports a similar ratio. The Committee also noted a 2022 study of inequities in stroke care access in New Zealand which reported that non-Europeans were less likely to achieve functional independence up to 12 months after suffering a stroke ([Thompson et al. Lancet Reg Health West Pac. 2022;20:100358](#)). The Committee noted that the same study reported that Māori and Pacific people had significantly reduced odds of a favourable outcome up to 12 months, and that Māori had higher odds of death at 12 months (adjusted odds ratio =1.76, 95% CI 1.07 to 2.89).

- 7.11. The Committee noted that smoking, high blood pressure, myocardial infarction (MI), exposure to household air pollutants and diabetes mellitus are all major risk factors for stroke.
- 7.12. The Committee noted that the currently available funded treatment for patients with minor ischaemic stroke or high-risk TIA is with immediate dual antiplatelet therapy with both clopidogrel and aspirin for two to three weeks, switching to single antiplatelet therapy after that time (usually clopidogrel, otherwise aspirin in the context of clopidogrel poor/non-responder). The Committee noted that although treatment with clopidogrel is effective over aspirin alone in patients with minor stroke or high-risk TIA, patients must have a functioning CYP2C19 gene for clopidogrel to be correctly transformed into its active metabolite and that those without correctly functioning CYP2C19 will not derive the same benefit from clopidogrel as those without mutations in this gene.
- 7.13. The Committee considered that the benefit of dual therapy over clopidogrel treatment alone is likely to be small. The Committee noted that long-term dual antiplatelet therapy is associated with an increased risk of haemorrhage, and that to maximise the effect of dual therapy and minimise risk of bleeding, short-term use of dual therapy was adopted followed by long term single anti-platelet therapy.
- 7.14. The Committee noted that CYP2C19 gene testing is not readily available across all New Zealand health centres and considered that rural patients would be even less likely to access testing compared to those living in urban centres. The Committee noted that a higher proportion of the Māori population in New Zealand live rurally and considered that this contributes further to inequities in access to sufficient care and treatment following minor stroke or TIA.
- 7.15. The Committee noted that a 2008 study by Lea et al. reported that the allele frequency for CYP2C19*2 variant, the most common loss-of-function variant for that gene, was 24% for Māori, versus 15% for a matched “Caucasian” population ([N Z Med J. 2008;121:33-7](#)). The Committee were also made aware of a 2015 study which reported that loss-of-function CYP2C19*2 allele was found in 47% of Māori and Pacific study participants, compared to 26% for Caucasians ([Larsen et al. Intern Med J. 2015;45:537-45](#)). The Committee noted that the difference in alleles only explained 3-4% of on-treatment platelet reactivity.
- 7.16. The Committee noted that Oceanic and East Asian patient populations are more likely to carry loss-of-function alleles for the CYP2C19 gene (estimated at 45% and 30%, respectively), and thus may benefit less from treatment with clopidogrel following a minor stroke or high-risk TIA ([Fricke-Galindo et al. Pharmacogenomics J. 2016;16:113-23](#); [Helsby et al. Br J Clin Pharmacol. 2016;82:1303-07](#)).
- 7.17. The Committee noted [data from PharmGKB](#), a pharmacogenomics knowledge resource, reporting allele frequency by biogeographical groups based on frequencies reported by reference studies. The Committee noted that the Central/South Asian biogeographical group was reported to have intermediate metaboliser frequency of 0.41, and that the East Asian biogeographical group was reported to have a frequency of 0.13 poor metaboliser and 0.46 intermediate metaboliser status. The Committee also noted that the “Oceanian” biogeographical group was reported to have a poor metaboliser phenotype frequency of 0.57, and an intermediate metaboliser status frequency of 0.37.

Health benefit

- 7.18. The Committee noted that ticagrelor is a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), and is an oral, direct acting selective and reversibly binding P2Y₁₂ receptor antagonist that prevents adenosine diphosphate (ADP)-mediated P2Y₁₂ dependent platelet activation and aggregation and ADP-induced signal transduction. The Committee noted that ticagrelor is not dependent upon CYP2C19 for activation. The Committee noted that ticagrelor is not Medsafe approved for the prevention of atherothrombotic events in those with minor stroke or high-risk TIA.

- 7.19. The Committee noted that the recommended dosing regimen for ticagrelor in the requested indication is 180 mg on day 1 as a loading dose, followed by 90 mg twice daily for 21 days total.
- 7.20. The Committee noted that ticagrelor is currently funded for the treatment of acute coronary syndrome, thrombosis prevention following neurological stenting (with the requirement for demonstrated clopidogrel resistance), percutaneous coronary intervention with stent deployment, and stent thrombosis. The Committee also noted that an application has previously been received to change ticagrelor or prasugrel Special Authority criteria to allow treatment guided by CYP2C19 genotyping for patients with acute coronary syndromes, and that this application was assessed by the Cardiovascular Subcommittee and deferred in [September 2017](#), and in [May 2019](#) pending evidence on the clinical outcomes associated with selecting antiplatelet agents based on genetic testing ([TALOR-PCI](#) and [POPular Genetics](#) trials).
- 7.21. The Committee noted that the European Stroke Organisation (ESO) recommends in its 2021 guidelines that dual anti-platelet therapy with clopidogrel and aspirin is preferred over the use of ticagrelor with aspirin for the prevention of atherothrombotic events following minor stroke or high risk TIA ([ESO 2021](#)). The Committee also noted a clinical pharmacogenetics implementation consortium guideline for CYP2C19 genotype and clopidogrel therapy which recommended that intermediate or poor metabolisers should be treated with prasugrel or ticagrelor, and that clopidogrel should be avoided ([Lee et al. Clin Pharmacol Ther. 2022;10.1002/cpt.2526](#)).
- 7.22. The Committee noted the following trials that provided evidence relating to the use of ticagrelor for minor stroke or TIA:
- 7.22.1. The THALES trial ([Johnston et al. N Engl J Med. 2020;383:207-17](#)): a randomised, placebo-controlled, parallel group, double-blind trial of 11,016 patients aged 40 years or older with either mild-to-moderate acute non-cardioembolic ischemic stroke (NIHSS score of 5 or less) or high-risk TIA (ABCD2 score 6 or higher) treated with ticagrelor plus aspirin or aspirin alone for 30 days, with an additional 30 day follow-up. There was a small absolute risk reduction supporting the use of ticagrelor (absolute risk reduction 1.1%). Patients in the ticagrelor group also had a higher incidence of bleeding compared to the aspirin alone group (0.5% versus 0.1%, respectively), and a higher rate of trial discontinuation due to bleeding events (2.9% in the ticagrelor group versus 0.6% in the aspirin alone group).
- 7.22.2. The CHANCE-2 trial ([Wang et al. N Engl J Med. 2021;385:2520-30](#)): a randomised, double-blind, placebo controlled trial of 6,412 patients aged 40 years or older with a minor ischemic stroke (NIHSS score of 3 or less) or TIA (ABCD2 score of 4 or more) who carried CYP2C19 loss-of-function alleles who were treated with either ticagrelor with aspirin or clopidogrel with aspirin for 21 days, with 90 day follow-up. The absolute risk reduction for stroke within 90 days was 1.6% in favour of ticagrelor. There was an increase in 'any bleeding' events with ticagrelor compared to clopidogrel (5.3% and 2.5%, respectively), but no difference in 'severe bleeding'.
- 7.23. The Committee noted the following additional studies relating to the use of ticagrelor for minor stroke and TIA:
- [Wang et al. BMJ. 2019;365:l2211](#)
 - [Wang et al. Stroke. 2022;101161STROKEAHA122038662](#)
 - [Yang et al. Front Neurol. 2020;11:534](#)
 - [Yang et al. Eur J Neurol. 2020;27:833-40](#)
 - [Amarenco et al. JAMA Neurol. 2020;78:1-9](#)

- [Amarenco et al. Stroke. 2020;51:3504-13](#)
- [Wang et al. JAMA Neurol. 2021;78:1091-8](#)
- [Johnston et al. Stroke. 2021;52:3482-9](#)

7.24. The Committee noted the following trials that provided evidence relating to the use of clopidogrel for minor stroke or TIA:

- 7.24.1. The POINT trial ([Johnston et al. N Engl J Med. 2018;379:215-25](#)): a randomised, double-blind, placebo-controlled trial investigating either clopidogrel with aspirin versus aspirin alone for minor ischemic stroke or high-risk TIA (N=2432). The primary efficacy outcome was the risk of a composite of major ischemic events, which was defined as ischemic stroke, myocardial infarction, or death from an ischemic vascular event, at 90 days.
- 7.24.2. Major ischemic events occurred in 121 patients (5.0%) receiving clopidogrel plus aspirin and in 160 patients (6.5%) receiving aspirin plus placebo (absolute risk reduction 1.5%; HR 0.75; 95% CI 0.59 to 0.95; P = 0.02), with most events occurring during the first week after the initial event. Major haemorrhage occurred in 23 patients (0.9%) receiving clopidogrel plus aspirin and in 10 patients (0.4%) receiving aspirin plus placebo (HR 2.32; 95% CI 1.10 to 4.87; P = 0.02).
- 7.24.3. The CHANCE trial ([Wang et al. N Engl J Med. 2013;369:11-9](#)): a randomised, double-blind, placebo-controlled trial in which 5170 Chinese patients received either clopidogrel with aspirin or placebo with aspirin within 24 hours of onset of minor stroke or TIA. The primary outcome was stroke (ischemic or haemorrhagic) during 90 days of follow-up.
- 7.24.4. Stroke occurred in 8.2% of patients in the clopidogrel–aspirin group, as compared with 11.7% of those in the aspirin group (absolute risk reduction 3.5%; HR 0.68; 95% CI 0.57 to 0.81; P<0.001). Moderate or severe haemorrhage occurred in seven patients (0.3%) in the clopidogrel–aspirin group and in eight (0.3%) in the aspirin group (P = 0.73); the rate of haemorrhagic stroke was 0.3% in each group.
- 7.24.5. A subgroup analysis of the CHANCE trial by genotype status ([Wang et al. JAMA. 2016;316:70-8](#)) reported that the use of clopidogrel in combination with aspirin compared to with aspirin alone reduced the risk of atherothrombotic events only in the subgroup of patients who were CYP2C19 metabolisers (poor/intermediate metabolisers absolute risk reduction with clopidogrel with aspirin 1.5% versus 5.8% in the CYP2C19 metaboliser group).
- 7.25. The Committee noted that participants in the CHANCE trial were primarily Chinese, and therefore would be expected to have a high proportion of intermediate or poor CYP2C19 metabolisers. The Committee noted that clopidogrel was still reported to be effective in this group of patients.
- 7.26. The Committee noted that there was one head-to-head trial of ticagrelor and aspirin versus clopidogrel and aspirin in those with minor stroke or TIA (CHANCE -2). The Committee considered this evidence to be of moderate quality due to the indirectness of evidence for a New Zealand population ie, Han Chinese who were carriers of CYP2C19 loss of function alleles.
- 7.27. The Committee noted the TAILOR-PCI trial ([Pereira et al. JAMA. 2020;324:761-71](#)) to determine if the effect of a genotype-guided oral P2Y12 inhibitor strategy on ischemic outcomes in CYP2C19 loss of function carriers after percutaneous coronary intervention. The Committee noted that among CYP2C19 loss of function carriers with acute coronary syndromes or stable coronary artery disease undergoing percutaneous coronary intervention, genotype-guided selection of an oral P2Y12 inhibitor (ticagrelor or clopidogrel), compared with conventional clopidogrel therapy without point-of-care genotyping, resulted

in no statistically significant difference in a composite end point of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia.

Suitability

- 7.28. The Committee noted that ticagrelor is taken twice daily, compared to once daily with clopidogrel, and that the risk of adverse bleeding events is higher with ticagrelor treatment.
- 7.29. The Committee noted that, ideally, patient's CYP2C19 metaboliser status would be tested using a rapid point-of-care test at first point of contact with the health system following a minor stroke or TIA in order to provide them with the most appropriate treatment options. The Committee noted that currently only some tertiary urban healthcare centres offer a non-point-of-care test (using the VerifyNow PRU Test), with variable wait times before results are made available.

Costs and savings

- 7.30. The Committee noted that after a 21-day treatment period with dual anti-platelet therapy post-stroke or TIA, patients may be offered ongoing treatment with either clopidogrel or aspirin monotherapy, and that most patients would be offered clopidogrel.
- 7.31. The Committee noted that the health sector impacts associated with strokes and TIAs were considerable, with people with strokes and TIAs requiring hospitalisation, inpatient rehabilitation and in some cases, residential care. The Committee considered that a reduction in recurrent stroke and TIA events among a high-risk patient group could represent a saving to the health sector.

Funding criteria

- 7.32. The Committee noted that patients who have undergone neurological stenting must demonstrate clopidogrel resistance using the P2Y12 (VerifyNow) assay or another appropriate platelet function assay in order to access ticagrelor. The Committee considered that due to the variability in availability in testing services, the potential week-long wait times for results, and the short treatment duration of ticagrelor for minor stroke or TIA, it would not be appropriate for access to ticagrelor to be restricted based on CYP2C19 metaboliser status.
- 7.33. The Committee considered that while it may be useful to know a patient's CYP2C19 metaboliser status, it is also important to elucidate comorbidity variables and possible lifestyle and medication changes in order to reduce the risk of acute and longer-term atherothrombotic events. The Committee also considered that there is not always a strong relationship between CYP2C19 genotype and clopidogrel metaboliser phenotype.
- 7.34. The Committee noted that clinicians would assess their patient's suitability for ticagrelor treatment on a case-by-case basis, based on their age, overall health status, comorbidities, and risk profiles. The Committee considered that ticagrelor may not be suitable for some patients due to the potential increase in bleeding risk and noted that some patients also experience intolerable breathlessness while on ticagrelor.

Summary for assessment

- 7.35. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for ticagrelor if it were to be funded in New Zealand for the prevention of atherothrombotic events following minor stroke or TIA. 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: <ul style="list-style-type: none"> • ischaemic stroke with NIHSS or 3 or less, OR • transient ischaemic attack with ACBD² score of 4 or higher
Intervention	Ticagrelor, in combination with aspirin <ul style="list-style-type: none"> • Recommended ticagrelor dosage on day 1 is 180mg, followed by 90mg twice daily for the remaining days of treatment – for a treatment duration of 21 days post-stroke/TIA.
Comparator(s)	Clopidogrel, in combination with aspirin, for 21 days post-stroke/TIA.
Outcome(s)	Reduced risk of new/recurrent stroke <ul style="list-style-type: none"> • Wang et al. NEJM. 2021;385: 2520-2530 reported that ticagrelor treatment was associated with a lower risk of new stroke within 90 days compared to clopidogrel, among patients, who were poor metabolisers of clopidogrel (HR=0.77; 95% CI, 0.64 to 0.94). • Among patients who are NOT poor/intermediate metabolisers of clopidogrel, no incremental benefit associated with ticagrelor.
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. Siponimod for the treatment of secondary progressive multiple sclerosis (SPMS)

Application

- 8.1. The Committee reviewed the application from Novartis New Zealand Limited for siponimod for the treatment of secondary progressive multiple sclerosis (SPMS).
- 8.2. The Committee also reviewed a submission in support of the funding of siponimod provided by Multiple Sclerosis New Zealand (MSNZ), which included consumer stories.
- 8.3. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

- 8.4. The Committee **recommended** that siponimod for the treatment of active SPMS be listed with a **low priority**, subject to Special Authority criteria.
- 8.5. The Committee **recommended** that Pharmac seek further advice from the Neurological Advisory Committee regarding appropriate Special Authority criteria.
- 8.6. In making this recommendation, the Committee 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.
 - The good quality, poor strength evidence that demonstrated the health benefit of siponimod in the treatment of SPMS.

Discussion

Māori impact

- 8.7. The Committee discussed the impact of funding siponimod for the treatment of SPMS on Māori health outcomes and Māori health areas of focus. The Committee noted that the prevalence of MS in Māori is substantially lower than that of non-Māori. It was considered that the impact of MS, when it occurs, is likely to be greater in Māori, noting the higher

representation of Māori in lower socioeconomic groups and the effect of this on functional needs and access to care and diagnostic support services.

Background

- 8.8. The Committee noted that Pharmac currently funds eight disease modifying treatments for relapsing remitting MS under Special Authority. One proposal for ocrelizumab for primary progressive MS (PPMS) has also been considered and is currently ranked as an options for investment. The Committee noted that Pharmac has not previously received a funding application for SPMS, nor does it fund any treatments specifically for SPMS.

Health need

- 8.9. The Committee noted that MS is an autoimmune, inflammatory, demyelinating disease of the central nervous system (CNS) that is a leading cause of disability in young adults. It was noted that the majority (85-90%) of MS patients are diagnosed with relapsing-remitting MS (RRMS), and that this is characterised by episodes of acute neurological deterioration (relapses), followed by partial or complete recovery (remission), and may later develop into SPMS with progressive decline. The Committee noted that SPMS is marked by fewer or no periods of remission and gradual neurological worsening with brain atrophy. It was noted that the remaining 10-15% of patients with MS are diagnosed with PPMS, which is characterised by continuous neurological worsening from the first onset of symptoms, without remission or relapse.
- 8.10. The Committee noted that the diagnosis of MS internationally, including SPMS, utilises specific diagnostic criteria known as the McDonald criteria, which include cerebrospinal fluid abnormalities, central nervous system (CNS) lesions separated in space and time, and continued disease progression – specifically, clinical evidence that the disease has progressed for at least one year from symptom onset. The Committee noted that under the McDonald criteria (last revised in 2017 [[Thompson et al. Lancet Neurol. 2018;17\(2\):162-73.](#)]), progressive disease (both primary and secondary) has a course characterised by steadily increasing objectively documented neurological disability independent of relapses (where fluctuations, periods of stability, and superimposed relapses may occur). The Committee noted that the change from RRMS to SPMS is a gradual process rather than an abrupt transition, with diagnoses often made retrospectively.
- 8.11. The Committee noted that the age and sex-standardised prevalence rate of MS in New Zealand is 73.1 per 100,000 (standardised to the European population) and the annual age standardised incidence is 3.3 per 100,000. The Committee noted that a latitudinal gradient exists with MS prevalence increasing threefold from the North (37 deg. S) to the South (48 deg. S) of NZ ([Alla et al. J Clin Neurosci. 2014;21:1288-91](#)). The Committee noted that the overall age and sex standardised prevalence of MS in Māori has been reported to be between 20.6 and 24.2 per 100,000 (approximately 3.6 times lower than that of non-Māori). The Committee noted that earlier regional surveys (1968-2001) all reported much lower, or zero, prevalence for Māori compared to non-Māori. The Committee considered that Māori ethnicity does not seem to be related to the latitudinal patterns of MS prevalence observed in New Zealand. The Committee noted that whilst it is well recognised that under-reporting is a factor in low disease prevalence in indigenous populations, differences in genetic factors and differing susceptibility to environmental factors are also likely to play a role ([Alla et al. J Clin Neurosci. 2014;21:1288-91](#); [Pearson et al. Mult Scler. 2014;20:1892-5](#); [Taylor et al. Multiple Sclerosis. 2010;16:1422-31](#)).
- 8.12. The Committee noted that the 2006 MS Prevalence Study identified 2917 people with MS, with 912 were listed as having SPMS. The Committee noted that, based on today's total NZ MS population being over 4000, MSNZ has calculated over 1250 people to have SPMS, with 632 of these individuals having an EDSS of 3.0-6.5 at any one time (MSNZ supplementary information).

- 8.13. The Committee noted that patients with SPMS experience wide-ranging symptoms and a high symptomatic burden throughout their disease course, including cognitive and memory impairment, loss of mobility, fatigue, pain, depression, bowel, bladder and sexual dysfunction, speech and auditory impairment, and oedema. It was noted that studies have demonstrated that patients with SPMS experience greater symptom severity than those with RRMS (Pike et al. 2015, [Gross et al. *Neuropsychiatr Dis Treat.* 2017;13:1349-57](#)). The Committee noted that the health-related quality of life of those with SPMS is reported to decline at a faster rate compared to those with RRMS, as people progress through EDSS states more quickly. It was also noted that the health-related quality of life may be worse in the same EDSS state for someone with SPMS compared to someone with RRMS ([McCrone et al. *Pharmacoeconomics.* 2008;26:847-60](#); [Orme et al. *Value Health.* 2007;10:54-60](#); Fisk et al. 2016).
- 8.14. The Committee also noted the consumer stories provided by MSNZ of New Zealanders living with SPMS, which described the significant impact this condition has on the lives of the individual and their family/whānau. The Committee noted that those with SPMS experience numerous debilitating physical and mental symptoms, substantial comorbidities, and significant disability which frequently requires support often needing to be provided by family and friends. The Committee considered that this further highlighted the severe unmet need for those with SPMS.
- 8.15. The Committee noted that caregivers of patients with MS have been reported to experience high levels of distress and reduced health related quality of life ([Figved et al, *J Neurol Neurosurg Psychiatry* 2007; 78:1097-1102](#)). Similarly, the Committee noted that the health related quality of life of children who have a parent with MS has also been reported to be impacted by the disease ([Yahav et al, *Mult Scler* 2005; 11:464-8](#)). The Committee noted that SPMS is associated with a high level of physical and mental impairment, and it would therefore be expected that many patients with SPMS would require caregivers, which is often provided by the person's family. It was also considered that those living rurally may be disproportionately impacted by SPMS due to reduced access to secondary care and specialised support services.
- 8.16. The Committee noted that there are currently no funded disease modifying treatments specifically for SPMS, but that people with RRMS who meet the funding criteria can continue to receive [funded treatment](#) until they surpass an Expanded Disability Status Scale (EDSS) score of 6.5. It was noted that people with SPMS are currently managed in primary care, predominantly due to the lack of funded disease modifying treatments neurologists could prescribe for the management of SPMS. The Committee considered that the funding of a treatment, such as siponimod, would result in people being under the care of a neurologist once again.
- 8.17. The Committee noted that this proposal aligns with the Government health priority of long-term conditions.

Health benefit

- 8.18. The Committee noted that siponimod is a selective sphingosine-1-phosphate receptor modulator that acts as a functional antagonist on S1P1 receptors on lymphocytes, thereby preventing egress from lymph nodes and reducing the recirculation of T cells into the CNS to limit central inflammation ([Mayzent SPC. EMC. DOR 2022](#)). The Committee noted that siponimod is [Medsafe approved](#) for the treatment of SPMS.
- 8.19. The Committee noted that siponimod treatment is to be initiated with a titration pack that lasts for five days, with the maintenance dose of 2 mg reached on day six. It was noted that the recommended maintenance dose is 1 mg daily for those with CYP2C9*2*3 or *1*3 genotype, and that siponimod is contraindicated in those with a CYP2C9*3*3 genotype.
- 8.20. The Committee noted the following evidence from the EXPAND trial:

- 8.20.1. The Committee noted that the EXPAND trial was an event- and exposure-driven, double-blind, placebo-controlled, phase III trial which investigated the efficacy of siponimod (n=1099) versus placebo (n=546) in patients aged 18 to 60 years with SPMS and an EDSS score of 3.0 to 6.5. The Committee noted that the primary outcome was time to 3-month confirmed disability progression (CDP), which was defined as a 1-point increase in EDSS if the baseline score was 3.0 to 5.0, or a 0.5-point increase if the baseline score was 5.5 to 6.5, confirmed at a scheduled visit at least 3 months later ([Kappos et al. Lancet. 2018;391:1263-73](#)).
- 8.20.2. The Committee noted that after a median time on study of 21 months (range 0.2 to 37.0), 288 (26%) of 1096 patients receiving siponimod and 173 (32%) of 545 patients receiving placebo had 3-month CDP (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.65 to 0.95; risk reduction [RR] 21%; P=0.013). The Committee noted that the risk of 6-month CDP was also reduced by siponimod (HR 0.74, 95% CI 0.60 to 0.92; RR 26%; P=0.0058) ([Kappos et al. Lancet. 2018;391:1263-73](#)).
- 8.20.3. The Committee noted that no significant difference was seen in the time to 3-month confirmed worsening of at least 20% from baseline in the timed 25-foot walk test (T25FW) for the overall population (HR 0.94, 95% CI 0.80 to 1.10; RR 6%; P=0.44) or for patients with a baseline EDSS score of 5.5 or lower (post-hoc analysis; P=0.25). The Committee noted that the change from baseline in T2 lesion volume was lower with siponimod than with placebo (adjusted mean over months 12 and 24 183.9mm³ vs 879.2mm³; between-group difference -695.3 mm³, 95% CI -877.3 to -513.3; P<0.0001) ([Kappos et al. Lancet. 2018;391:1263-73](#)).
- 8.20.4. The Committee noted that the incidence of adverse events in the siponimod versus placebo groups was 975 (89%) versus 445 (82%) overall and 197 (18%) vs 83 (15%) for serious adverse events, respectively. The Committee noted that lymphopenia, increased liver transaminase concentrations, bradycardia and bradyarrhythmia at treatment initiation, macular oedema, hypertension, varicella zoster reactivation, and convulsions occurred more frequently with siponimod than with placebo ([Kappos et al. Lancet. 2018;391:1263-73](#)).
- 8.20.5. The Committee also noted the results of the secondary analyses of the EXPAND trial, which reported that between-group differences in mean change from baseline in Symbol Digit Modalities Test (SDMT) scores were significantly better in siponimod- vs placebo-treated patients at month 12 (difference 1.08 [95% CI 0.23 to 1.94]; P=0.0132), month 18 (1.23 [0.25 to 2.21]; P=0.0135), and month 24 (2.30 [1.11 to 3.50]; P=0.0002). The Committee noted that siponimod-treated patients were at significantly lower risk for having a 4-point sustained decrease in SDMT score (HR 0.79 [0.65 to 0.96]; P=0.0157), while their chance for having a 4-point sustained increase in SDMT score was higher (HR 1.28 [1.05 to 1.55]; P=0.0131). ([Benedict et al. Neurology. 2021;19:e376-86](#)).
- 8.20.6. The Committee was made aware of an open-label extension analysis of EXPAND core and extension data up to >5 years, which reported the long-term efficacy and safety of siponimod in patients with SPMS. The Committee noted that participants receiving placebo during the core trial were switched to siponimod (placebo-siponimod group) and those on siponimod continued the same treatment (continuous siponimod group). The Committee noted that continuous siponimod treatment reduced the risk of 6-month CDP by 22% (HR 0.78, CI 0.66 to 0.92, P=0.0026) and 6-month confirmed worsening in CPS by 23% (HR 0.77, CI 0.65 to 0.92, P=0.0047) versus the placebo-siponimod group. The Committee noted that no new, unexpected safety signals for siponimod were identified over the long term ([Cree et al. Mult Scler. 2022;28:1591-1605](#)).
- 8.21. The Committee considered the EXPAND trial to be of good quality but poor strength due to the short duration of trial in comparison to the long-term condition. The Committee considered that the EXPAND trial demonstrated that three months of siponimod treatment reduced the risk of CDP, worsening in cognitive processing speed, relapses, and magnetic resonance imaging (MRI) measures of brain atrophy and inflammation versus placebo in

SPMS. The Committee considered that the benefit of siponimod was demonstrated in the EDSS range of 3.0 to 6.5. The Committee considered that siponimod had no significant effect on the main secondary endpoint (T25FW), an appropriate and well-established measure of gait velocity with a high association with the EDSS; however, T25FW does not include the person's ability to vary gait to perform different tasks needed during walking. The Committee considered that the side effect profile of siponimod appears similar to that of other MS treatments and are relatively easy to monitor, however also noted that siponimod may increase the risk of contracting infections such as COVID-19 ([Skorić et al. Mult Scler Relat Disord. 2022;57](#)).

- 8.22. The Committee considered that the pre-existing use of disease-modifying therapies may have confounded the EXPAND trial results, however that this would likely reflect the actual population if siponimod were funded as many people would be expected to have been previously treated with a disease-modifying treatment for RRMS.
- 8.23. The Committee considered that the length of the EXPAND trial was not sufficient to assess the long-term efficacy of siponimod in the treatment of SPMS. The Committee noted comments made by the National Institute for Health and Care Excellence (NICE) on the primary outcome of the EXPAND trial, which assessed disability progression confirmed after three months and not after six months as recommended by the European Medicines Agency; rather, 6-month CDP was a secondary outcome. The Committee also considered there to be a paucity of evidence regarding the long-term effects of lymphocyte depletion, however members considered information could be extrapolated from other immune modulators and immunosuppression and transplant patients to approximate this.
- 8.24. The Committee also noted the comments made by other Health Technology Assessment agencies in the evaluation of siponimod. It was also noted that NICE highlighted that CDP was based on the EDSS score and it is recognised that this does not adequately assess upper limb function and cognitive impairment. The Committee noted NICE's comments on the post hoc subgroup analysis of patients, which stated that since the study was neither planned nor powered for this post hoc analysis, these results should be interpreted with caution.

Suitability

- 8.25. The Committee noted that siponimod is administered orally once daily at approximately the same time each day. The Committee noted that the tablets should be swallowed whole with water, which may be challenging for patients who have difficulty with swallowing medicines. The Committee noted that, as siponimod can be self-administered by the patient or caregiver in the community, the burden of treatment delivery and need for repeated attendance at a hospital or outpatient facility would be minimised.
- 8.26. The Committee noted that the individual's CYP2C9 genotype must be determined before initiation of treatment with siponimod. The Committee considered that this genotype testing is not currently available in New Zealand, and currently if CYP2C9 tests are required they are sent to Australia to be processed. The Committee considered that approximately 5.5% of the New Zealand Europeans and 0.4% of Māori are estimated to have the CYP2C9*3*3 genotype in which siponimod treatment is contraindicated.

Cost and savings

- 8.27. The Committee noted that disease management costs for MS have long been noted to increase with disease progression to higher EDSS scores. The Committee noted that if siponimod delays the rate of disease progression, then the impact on the health system may also be delayed as patients would spend relatively more time in better health. The Committee also noted the Economic Burden Report provided by MSNZ.
- 8.28. The Committee noted that if siponimod were to be funded, more people would require an MRI scan to confirm a SPMS diagnosis to determine whether they are eligible, which may

have a substantial resource impact for Te Whatu Ora - Health NZ hospitals. The Committee considered that having an available treatment for SPMS may increase the diagnoses of SPMS. The Committee noted that an available treatment for SPMS would mean that individuals would remain under the care of a neurologist.

- 8.29. The Committee considered that genotype testing would create an additional cost, with CYP2C9 tests estimated to cost approximately \$2000 AUD per test. The Committee noted and agreed with the supplier's assumption that 12% of patients would require a lower 1 mg dose (and therefore require the 0.25 mg formulation) based on them being classed as 'intermediate metabolisers' according to their CYP2C9 genotype.
- 8.30. Members considered the cost-effectiveness assumptions to be broadly reasonable. Members specifically noted that the assumption used in previous Pharmac PPMS modelling that patients could not move to a less severe EDSS state would be appropriate in the modelling of SPMS as well.

Funding criteria

- 8.31. The Committee considered that MS phenotypes are not always distinct or clear, and therefore that funding criteria should be carefully considered to ensure those who would most benefit are not excluded. The Committee noted that the evidence suggests that siponimod would be most effective in people with active SPMS with an EDSS of 3.0 to 6.5; members considered that an important outcome of siponimod treatment was quality of life. The Committee **recommended** that specialist advice be sought from the Neurological Advisory Committee regarding appropriate Special Authority criteria for siponimod, in particular, the renewal criteria and the appropriateness of measures such as EDSS or quality of life.

Summary for assessment

- 8.32. The Committee considered that the table 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.

Population	Patients with SPMS with an EDSS score of 3.0-6.5 [this may be revised following advice from the Neurological Advisory Committee] Patients must have a history of RRMS and documented EDSS progression in the past two years (ie. active progressive disease).
Intervention	Daily 2 mg siponimod, or 1 mg for those with the CYP2C9*2*3 or 1*3 genotype (following titration period) taken orally until disease progression past EDSS 6.5
Comparator(s) (NZ context)	Best supportive care. There are currently no funded disease-modifying treatments for SPMS
Outcome(s)	<ul style="list-style-type: none"> Reduction in rate of disease progression as measured by EDSS, leading to health-related quality of life improvements and lower mortality risk.
<p><u>Table definitions:</u></p> <p>Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)</p> <p>Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).</p> <p>Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).</p> <p>Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.</p>	

9. Cannabidiol oral liquid (Epidyolex) - Adjunctive therapy for individuals with Dravet Syndrome

Application

- 9.1. The Committee reviewed the clinician application made on behalf of the Paediatric Neurology Network and the New Zealand League Against Epilepsy for cannabidiol oral liquid (Epidyolex) for adjunctive therapy for individuals with Dravet syndrome who are two years and older and who have ongoing seizures despite trials of sodium valproate and clobazam.
- 9.2. The Committee noted that the application was supported by Epilepsy New Zealand and the Paediatric Society of New Zealand.
- 9.3. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

- 9.4. The Committee **recommended** that the Epidyolex brand of cannabidiol oral liquid be listed in the Pharmaceutical Schedule for the treatment of Dravet Syndrome with a **high priority**, subject to the following Special Authority criteria:

CANNABIDIOL (Epidyolex) – adjuvant treatment of Dravet syndrome

Initial application – Applications only from a paediatric neurologist or practitioner on the recommendation of a paediatric neurologist. Approvals valid for 6 months.

1. Patient has a confirmed diagnosis of Dravet syndrome, requiring adjuvant treatment; and
2. Seizures have been inadequately controlled with appropriate courses of sodium valproate and clobazam.

Renewal – Applications from any relevant practitioner. Approvals valid for 6 months where the treatment remains appropriate and the patient is benefitting from the treatment.

- 9.4.1. In making this recommendation, the Committee considered that:

- Patients with Dravet syndrome, their caregivers and family/whānau have high health needs due to the significant impact of the condition
 - There is good quality evidence of benefits from Epidyolex in terms of seizure frequency and improvements in measures important to people with Dravet syndrome and their caregivers
 - There may be cost savings and benefits through a reduction in seizures due to the high health resource use required
- 9.5. The Committee noted that this recommendation is subject to the Epidyolex brand of cannabidiol oral liquid receiving Medsafe approval.
- 9.6. The Committee considered that Pharmac should send a copy of this record, documenting its discussion of this item, to the Neurological Advisory Committee for noting.

Discussion

Māori impact

- 9.7. The Committee noted that there is no published epidemiological data for Māori with Dravet syndrome but considered it was probable that Māori children with Dravet Syndrome would experience worse outcomes than non-Māori children. There is evidence that Māori patients experience a higher burden of epilepsy compared to the general New Zealand population in terms of access to treatment, incidence of status epilepticus, and mortality.

Background

- 9.8. The Committee noted that PTAC briefly considered medicinal cannabis for this indication in its [March 2021](#) horizon scan. At that time, PTAC noted that England and Wales (NICE) had reviewed evidence that appeared to be of reasonable quality for cannabidiol (Epidyolex: 100 mg/ml CBD) in conjunction with clobazam in patients with paediatric epilepsy syndromes and that the NICE had recommended cannabidiol as a treatment option for these rare syndromes ([NICE December 2019a](#); [NICE December 2019b](#)). At that time, PTAC considered that the submission reviewed by NICE was supported by evidence which, if accompanied by the appropriate application content, might meet Pharmac's application requirements. The Committee considered that it would be reasonable to consider Epidyolex for the adjunctive therapy of seizures associated with Developmental and Epileptic Encephalopathies (eg Lennox-Gastaut syndrome), if Pharmac were to receive an application for that indication.

Health Need

- 9.9. The Committee noted that Dravet syndrome is a Developmental and Epileptic Encephalopathy (DEE), one of a group of severe epilepsies characterised by frequent seizures which are difficult to treat and lead to significant developmental delays. Dravet syndrome is generally linked to a mutation in the sodium channel gene SCN1A, and is associated with prolonged seizures, behavioural problems, increasing comorbidity over the person's lifetime, and increased risk of unexpected death. The Committee considered it reasonable to assume that the incidence of Dravet syndrome is five per 100,000 live births, based on the applicant estimate of 50 children aged zero to 16 years in New Zealand with Dravet syndrome at any one time. The Committee noted that diagnosis usually occurs between two and five years of age, and that the average patient age is 6.5 years. The Committee noted that people with Dravet syndrome in New Zealand are usually under the care of a paediatrician and paediatric neurologist, and that adult patients would be transferred to receive ongoing care from a neurologist.
- 9.10. The Committee noted that people with Dravet syndrome have very high health needs with many children, teenagers and adults being dependent on caregivers. The Committee noted there is evidence that people with Dravet syndrome can experience a median convulsive

seizure frequency of 13 seizures per month (range 3.7 to 1717; [Devinsky et al. N Engl J Med. 2017;376:2011-20](#)) and that frequent seizures result in recurrent hospitalisations, especially due to convulsive status epilepticus which is common in Dravet syndrome ([Li et al. Epilepsia. 2021;62:2205-17](#)). Members considered that the frequency and impact of seizures (eg on behaviour) ranges, but in general, that the health need and health resource usage (eg paediatric neurologist, emergency department (ED), days in hospital, interventions) is high in Dravet syndrome. The Committee noted that the reported Dravet-specific Sudden Unexplained Death in Epilepsy (SUDEP) rate of 9.32 per 1000-person-years is considerably higher than the 5.1 SUDEP rate per 1000-person-years for adults with refractory epilepsy, and that patients with Dravet syndrome have an annual mortality rate of 1.58% ([Cooper et al. Epilepsy Res. 2016;128:43-7](#)). The Committee noted that the reduction in health-related quality of life in Dravet syndrome is well documented ([Brunklaus et al. Epilepsia. 2011;52:1476-82](#); [Lagae et al. Dev Med Child Neurol. 2018;60:63-72](#); [Sinoo et al. Epilepsy Behav. 2019;90:217-27](#)).

- 9.11. The Committee noted the effect of Dravet syndrome on the health of the family/whānau is substantial, including caregiver stress, depression, anxiety, fatigue and poor sleep. The Committee noted that convulsive seizures and intellectual disability in the person with Dravet syndrome are major contributors to these impacts. The Committee noted that the high number of ED attendances, and hospital admissions [including intensive care unit (ICU) admissions] due to episodes of status epilepticus have substantial social, financial and health-related impacts for family/whānau (including parents and siblings) in terms of caregiving, employment, sleep, free time, emotional stress, and mental and physical health. The Committee noted that in the [December 2019](#) NICE review of cannabidiol for Dravet syndrome, the company scenario analysis using a value of 1.8 carers per patient was considered preferable.
- 9.12. The Committee noted that there is no published epidemiological data for Māori with Dravet syndrome but considered it was probable that Māori children with Dravet Syndrome would experience worse outcomes than non-Māori children given the evidence for epilepsy in Māori. The Committee noted that the overall prevalence of epilepsy for Māori is similar to that of European or other population groups ([Ali et al. Neurology. 2021;97:e1933-41](#)), however, Māori patients experience a higher burden of epilepsy, being less likely to receive treatment for epilepsy ($P = 0.024$) and having higher mortality (hazard ratio [HR]: 1.41) compared to the general New Zealand population ([Hamilton et al. Epilepsia. 2020;61:519-27](#)). The Committee noted that the age-adjusted incidence of status epilepticus was higher in Māori (29.31 per 100,000 per year) than in patients of European (19.13 per 100,000/year) or Asian or other descent (17.76 per 100,000/year) ([Bergin et al. Epilepsia. 2019;60:1552-64](#)).
- 9.13. The Committee noted that the treatment of Dravet syndrome, a lifelong condition affecting young children, aligns with the overarching Government health priority of child wellbeing and Pharmac's specific health priority for the treatment of neurological disease (a long-term condition). The Committee considered that people with Dravet syndrome in rural or high deprivation communities would have greater barriers to access to hospitals and specialists for care than people with Dravet syndrome living in urban communities.
- 9.14. The Committee noted that clobazam or sodium valproate, or both, are used for first-line treatment of seizures in Dravet syndrome, however, most people (90%; [Ligae et al. Seizure. 2019;65: 72-79](#)) have disease that is refractory to these treatments. The Committee noted that topiramate, levetiracetam and a ketogenic diet are second-line options, although funded support for a ketogenic diet for this population is only available for a very limited number of people and not in all areas across New Zealand. The Committee noted that stiripentol is funded for Dravet syndrome following use of four prior therapies but is not widely used. The Committee considered that this is likely because of its undesirable adverse effect profile for patients/families and that there may be challenges involved in the optimal titration for benefit and adverse effect tolerance, The Committee noted that people with Dravet syndrome experience diminishing returns from each subsequent treatment and move through different anti-epilepsy drugs (AEDs) relatively quickly if they

receive insufficient clinical benefit. The Committee noted that AEDs acting on the sodium channel are inappropriate for use in Dravet syndrome. The Committee considered that while treatments are currently funded and used, there is a lack of effective funded treatments for Dravet syndrome.

Health Benefits and Suitability

- 9.15. The Committee noted that cannabidiol (CBD) is a phytocannabinoid derived from *Cannabis sativa* that has antiseizure activity but is structurally distinct from other AEDs. The Committee noted that it does not convey psychoactive effects as it does not contain tetrahydrocannabinol (THC). The Committee note that cannabidiol has novel multimodal mechanisms of action involving the G-protein coupled receptor 55 (GPR55) and the transient receptor potential vanilloid1 (TRPV1), modulates adenosine uptake, and causes minimal activation of the cannabinoid receptors CB1 or CB2 in usual prescribed doses ([Devinsky et al. *Epilepsia*. 2019;60:294-302](#)). The Committee considered that the potential for abuse by others was low due to these receptor differences. The Committee considered that the novel mechanism of action of cannabidiol may appeal, especially where families feel failed by conventional medicines. The Committee considered that, if funded, it would be important to fund a pharmaceutical grade cannabidiol product (ie approved by Medsafe as a medicine).
- 9.16. The Committee noted that Epidyolex (cannabidiol oral solution) has been submitted to Medsafe but is not yet approved. The Committee noted that Epidyolex is administered twice daily using a syringe according to weight-based dosing. The Committee considered that caregivers of children with Dravet syndrome would be familiar with this administration technique and that the treatment would be easy to store and administer.
- 9.17. The Committee noted evidence from the multinational, randomised (1:1), double-blind, placebo-controlled GWPCARE1 trial Part B which included 120 children and young adults with Dravet syndrome whose seizures were not controlled by their current AED regimen and who had four or more convulsive seizures during baseline period ([Devinsky et al. *N Engl J Med*. 2017;376:2011-20](#)). The Committee noted that participants had mean age of 9.8 years (range 2.3 to 18.4), had previously tried median four AEDs, were taking a median of three AEDs, and had median baseline convulsive-seizure frequency 13.0 seizures per month (range, 3.7 to 1717). Trial treatment was either Epidyolex cannabidiol oral liquid 20 mg/kg/day or placebo for 14 weeks. The Committee considered this trial included a diverse population whose baseline seizures per month ranged widely but included those with very high frequency (over 1,700) and whose disease had not resulted in very early death.
- 9.17.1. The Committee noted that the primary endpoint was the percentage change in convulsive seizure frequency, with median change of -38.9% (interquartile range, -69.5 to -4.8) from baseline with cannabidiol vs -13.3% (-52.5 to 20.2) with placebo. The Committee noted that the convulsive seizure frequency in the cannabidiol group decreased from a median of 12.4 seizures/month (range, 3.9 to 1717) at baseline to 5.9 (range, 0.0 to 2159), change in seizure frequency, -22.8% (95% CI, -41.1 to -5.4). There was no significant reduction in nonconvulsive seizures. The Committee noted that a 50% or greater reduction in convulsive-seizure frequency during the treatment period was reported in 43% cannabidiol vs 27% placebo (odds ratio, 2.00; 95% CI, 0.93 to 4.30; P=0.08). The Committee considered that these reductions in convulsive seizure frequency could be very meaningful for some people but that the impact of this reduction may be slightly less so for those with a large number of ongoing seizures per month.
- 9.17.2. The Committee noted that the Caregiver Global Impression of Change (CGIC, 7-point scale) was improved in 37/60 (62%) in the cannabidiol group vs 20/58 (34%) in the placebo group (P=0.02). The Committee noted that there were no significant between-group differences in sleep-disruption score, sleepiness scale score, Quality of Life in Childhood Epilepsy score, behaviour scale score, or hospitalisations due to epilepsy.

- 9.17.3. The Committee note that adverse events occurred more frequently in the cannabidiol group than in the placebo group, and that these included diarrhoea, vomiting, fatigue, pyrexia, somnolence (36%), and abnormal liver function tests results (93% vs 75%, respectively) especially in patients receiving concomitant sodium valproate. The Committee noted that eight cannabidiol patients and one placebo patient withdrew from the study due to adverse events.
- 9.18. The Committee noted evidence from the multinational, double-blind, placebo-controlled, randomised (1:1:1) trial GWPCARE2 trial in 199 patients aged 2 to 18 years with Dravet syndrome and at least four convulsive seizures during the baseline period while receiving at least one AED ([Miller et al. JAMA Neurol. 2020;77:613-21](#)). The Committee noted that the trial included a similar patient group as the previously reviewed evidence (median age 9.3 years at entry) and that patient received either Epidyolex (cannabidiol oral liquid) 10 mg/kg/day (CBD10), 20 mg/kg/day (CBD20), or matched placebo for 14 weeks.
- 9.18.1. The Committee noted that the primary outcome, convulsive seizure frequency compared with baseline, was reduced by 48.7% in CBD10 group and by 45.7% in the CBD20 vs 26.9% in the placebo group; a 29.8% reduction from placebo (95% CI, 8.4%-46.2%; P = 0.01) for CBD10 and a 25.7% reduction (95% CI, 2.9%-43.2%; P = 0.03) for CBD20 vs placebo, respectively. The Committee noted that the proportion of patients with at least a 50% reduction in convulsive seizure activity was 43.9% (n = 29) with CBD10 (P = 0.03), 49.3% (n = 33) with CBD20 (P = 0.007), and 26.2% (n = 17) with placebo.
- 9.18.2. The Committee noted that patients reported to be slightly improved, much improved, or very much improved (as measured by the CGIC scale at last visit) included 27/65 patients in the placebo group, 45/66 in the CBD10 group (P < .001), and 40/66 in the CBD20 group (P = 0.03).
- 9.18.3. The Committee noted that the most common adverse events were decreased appetite, diarrhoea, somnolence, pyrexia, and fatigue. The Committee noted that more adverse events were reported with the higher cannabidiol dose although considered that some patients may benefit from higher doses and tolerate additional adverse events. The Committee considered these results indicated no global difference in dose and that adverse events appeared balanced with benefits.
- 9.19. The Committee noted evidence from an open label, multicentre, extension study (GWPCARE5) that included 264 patients (efficacy population n=104) with Dravet syndrome that was inadequately controlled by at least one concurrent AED who completed treatment in GWPCARE1 Part A or B, or the GWPCARE2 study. ([Devinsky et al. Epilepsia. 2019;60:294-302](#)). The Committee noted that patients were median age 9.3 years at entry and were receiving median 3.0 concomitant AEDs. Patients received oral cannabidiol of mean modal dose 21.2 mg/kg/day for median 274 days (range 1-512).
- 9.19.1. The Committee noted the interim results reported that, during weeks 1-12, the median reduction in monthly convulsive seizure frequency from baseline was 37.5% (a reduction from 12.4 to 7.5 seizures per month) and that this reduction remained consistent. The Committee noted that more than 40% of patients had a 50% or greater reduction in convulsive seizures and in total seizures at each 12-week follow up window (reductions observed through 48 weeks) and at least 80% of patients/caregivers reported improvement in overall condition after 24, 36 and 48 weeks of treatment using the Subject/Caregiver Global Impression of Change (S/CGIC) scale. The Committee noted that 19 (7.2%) patients discontinued due to adverse events and there were two deaths due to Sudden Unexplained Death in Epilepsy (SUDEP), both considered unrelated to treatment. Members considered that this provided evidence of a sustained effect (even if not statistically significant) and meaningful reductions in seizure frequency.
- 9.19.2. The Committee noted a subsequent publication from the open-label GWPCARE5 extension study after median treatment of 444 days (range 18-1535) in 315 patients who received Epidyolex (cannabidiol oral liquid) 22 mg/kg/day (2.5-30) mg/kg/day ([Scheffer et](#)

[al. *Epilepsia*. 2021;62:2505-17](#)). Committee considered that the adverse event profile was similar to that seen in earlier reports with about a 9% dropout rate due to adverse events and noting the association between abnormal liver function tests and concomitant sodium valproate use. The Committee noted the S/CGIC scale scores reported improvement that was sustained out to week 156.

- 9.20. The Committee noted evidence from Trinka et al. ([Epilepsia. 2013;54: 495-501](#)) which reported that individuals with seizure-free epilepsy had a lower standardised mortality ratio compared to individuals with not-seizure-free epilepsy. However, the Committee considered that it was unknown whether cannabidiol was associated with a reduction in the risk of mortality for people with Dravet syndrome, noting that the reduction in the risk of mortality from a reduction in seizures would be difficult to quantify in the context of a large number of ongoing seizures and that the clinical trial data was limited by relatively short trial durations.
- 9.21. The Committee noted results from a safety analysis of an open-label trial which included 162 patients [33 (20%) of which had Dravet syndrome] aged 1-30 years with severe, intractable, childhood-onset, treatment-resistant epilepsy receiving stable doses of AEDs ([Devinsky et al. *Lancet Neurol*. 2016;15:270-8](#)). Patients were given oral cannabidiol at 2-5 mg/kg per day, up titrated until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg per day as add-on therapy to other treatments including stiripentol. The median monthly frequency of motor seizures was 30.0 [interquartile range (IQR) 11.0-96.0] at baseline and 15.8 (5.6-57.6) over 12-weeks treatment; median reduction in monthly motor seizures was 36.5% (IQR 0-64.7). Members noted that the carers of patients in this study were pleased with the treatment and members considered that a greater level of sedation in the context of a high number of seizures may be perceived as beneficial.
- 9.22. The Committee also noted the following evidence:
- [Laux et al. *Epilepsy Res*. 2019;154:13-20](#)
 - [Devinsky et al. *Neurology*. 2018;90:e1204-e1211](#)
 - [Ben-Menachem et al. *CNS Drugs*. 2020;34:661-72](#)
 - [Klotz et al. *CNS Drugs*. 2021;35:1207–15](#)
 - [Strzelczyk et al. *Neurol Res Pract*. 2022; 4: 22](#)
 - [Lo et al. *Clin Ther*. 2021;43:1861-76.e16](#)
 - [Goncalves et al. *Epilepsy Behav*. 2021;122:108206](#)
- 9.23. Overall, the Committee considered that the evidence for Epidyolex (cannabidiol oral liquid) in Dravet syndrome from several high-quality randomised controlled trials demonstrated its effectiveness for this indication in terms of a reduction in the number of convulsive seizures and in multiple health-related quality of life domains of importance to patients and their caregivers/families. However, the Committee considered that its long-term effects were unknown, including any reduction in the risk of mortality, SUDEP, or neurological deterioration. The Committee considered that the quality of the trials was high given the outcomes were difficult to define in this complex condition. The Committee noted that the therapeutic effect was strong vs placebo for a reduction in seizure frequency and considered the adverse event profile was well described, including somnolence and the liver function test abnormalities associated with concurrent sodium valproate. The Committee considered that complete seizure freedom appeared uncommon with Epidyolex in Dravet syndrome.

Costs and Savings

- 9.24. The Committee noted there was some evidence reporting that fewer seizures conveyed a reduction in emergency service usage ([Ligae et al. Seizure. 2019;65: 72-79](#)). However, the key clinical trial evidence reported no reduction in hospitalisation due to epilepsy with Epidyolex (cannabidiol oral liquid) ([Devinsky et al. N Engl J Med. 2017;376:2011-20](#)), although reduced inpatient hospitalisations was one of many secondary endpoints that the study was not powered to detect. The Committee considered that the limited evidence made it difficult to quantify potential health sector savings, although a reduction in Emergency Department visits, Paediatric Intensive Care Unit admissions, and hospitalisations was probable depending on an individual patient's baseline seizure rate. Members considered that these savings could be substantial.
- 9.25. The Committee considered that there was medium quality evidence for a health benefit (improved health-related quality of life) for family, whānau or wider society. However, it was unclear if this would be associated with a reduction in the number of caregivers required per patient or other health-related savings (eg relating to respite care, hospital admission costs, or parental health).
- 9.26. The Committee considered it would be reasonable for the use of Epidyolex (cannabidiol oral liquid) to be positioned after sodium valproate and clobazam (ie second line), noting that requiring use of other AEDs first (eg levetiracetam or topiramate) would reportedly be unlikely to convey sufficient benefits for most patients with Dravet syndrome and therefore would only be additional treatment steps to move through prior. The Committee considered that uptake would likely be 100% among patients with Dravet syndrome given the likely interest in trying cannabidiol and the known side effect profile of stiripentol. The Committee considered that clobazam would likely be preferred over sodium valproate for combination therapy with Epidyolex (cannabidiol oral liquid) due to liver function abnormalities reported when used with sodium valproate.
- 9.27. The Committee considered it reasonable to assume that 50 patients with Dravet syndrome would start Epidyolex (cannabidiol oral liquid) in year one of funding, with three new patients per year in subsequent years. The Committee considered that it was reasonable to base patient number estimates on the assumption that 90% of patients with Dravet syndrome would have disease that is refractory to first line therapy. Members considered that the risk of those outside the intended patient population receiving treatment was low given that access to cannabidiol would be via a paediatric neurologist.
- 9.28. The Committee considered that, due to the complexities and high need/severity of Dravet syndrome, assessment of ongoing funded treatment should be based on practitioner and patient/family assessment of meaningful benefit rather than a particular reduction in seizure frequency (eg the trial outcome of a $\geq 25\%$ reduction in seizures, which may be too high a threshold to detect a meaningful reduction in seizures in this context). The Committee considered that the renewal criteria should reflect this and consequently that discontinuation from funded treatment would be less than that reported in the clinical trials. The Committee considered it might be reasonable to assume long-term discontinuation from cannabidiol of 5% per year, noting that available data is short-term and suggests stabilisation to this level after two years. The Committee considered that it would be reasonable to reassess ongoing treatment every six or 12 months as people with Dravet syndrome would be routinely assessed this frequently.

Summary for assessment

- 9.29. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for Epidyolex (cannabidiol oral liquid) if it were to be funded in New Zealand for Dravet syndrome. 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	Individuals with diagnosed Dravet syndrome, who are two years and older and have ongoing seizures despite trials of sodium valproate and clobazam.
Intervention	Epidyolex brand of cannabidiol oral liquid taken as a second-line AED, as an adjunctive therapy in addition to other AEDs. Initial Epidyolex dosage of 2.5 mg/kg per day, increasing to a recommended dosage of 10-20 mg/kg per day. To be taken indefinitely if tolerated and efficacious.
Comparator(s)	Other second-line AEDs for Dravet syndrome - topiramate and levetiracetam.
Outcome(s)	Outcomes of interest may include: <ul style="list-style-type: none"> • Reduction in the frequency of <u>convulsive</u> seizures. • Improved health-related quality of life • Improvement in Caregiver Global Impression of Change • Potential reduction in ED visits, ICU admissions and hospitalisations
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. Daily Essential Nutrients for the treatment of ADHD for individuals who have experienced a poor response to an adequate trial of both a stimulant medication and atomoxetine

Application

- 10.1. The Committee reviewed the resubmission application from a researcher and a clinician for Daily Essential Nutrients in the treatment of ADHD for individuals who have experienced a poor response to an adequate trial of both a stimulant medication and atomoxetine or who have experienced intolerable adverse effects. This was an amended application related to an initial application by one of the same submitters in 2016.
- 10.2. The Committee noted that a letter of support from ADHD New Zealand, as well as consumer stories were included in the application.
- 10.3. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

- 10.4. The Committee **recommended** that Daily Essential Nutrients for the treatment of attention deficit and hyperactivity disorder (ADHD) be listed with a **low priority** subject to the following Special Authority criteria:

Initial application from a psychiatrist, or on the recommendation of a psychiatrist. Approvals valid for 24 months.

All of the following:

1. Patient has ADHD (Attention Deficit and Hyperactivity Disorder); and
2. Patient is diagnosed according to DSM-5 or ICD 11 criteria; and
3. Patient has not received effective response or has experienced unacceptable side effects from optimal treatment with atomoxetine, methylphenidate hydrochloride (any form) or dexamfetamine.

Renewal from a relevant practitioner. Approvals valid for 24 months.

1. The treatment remains appropriate, and the patient is benefiting from treatment

- 10.5. In making this recommendation, the Committee considered:

- the high health need and lack of funded alternative options for individuals with ADHD for whom currently funded treatment options are not effective or are intolerable;

- the observed positive effect of Daily Essential Nutrients on Clinical Global Impression scores for patients with ADHD in clinical trials;
 - the apparent lack of benefit of Daily Essential Nutrients on ADHD specific outcome measures in clinical trials;
 - the high applicability of the clinical trial results to the New Zealand population;
 - the lack of long-term (longer than 12 months) safety and toxicity data.
- 10.6. The Committee noted that this recommendation is subject to Daily Essential Nutrients receiving Medsafe approval for clinical use.

Discussion

Māori impact

- 10.7. The Committee noted that the [New Zealand Health Survey 2018/19](#) reported that the prevalence of attention deficit and hyperactivity disorder (ADHD) in Māori children was 2.8% and that Māori children were not significantly more likely to have ADHD compared with non-Māori children (adjusted prevalence ratio 1.09; 95% CI 0.60 to 1.98).
- 10.8. The Committee considered that nutrient intervention for mental health issues may be preferred by Māori patient populations and may be well accepted in Māori cultural models of wellbeing. The Committee considered that focusing on nutrition to improve mental health is an important step in upholding Mātauranga Māori and noted that the applicants stated that participants in their own research had a higher Māori representation than predicted from census patient population projections.
- 10.9. The Committee noted that access to mental health services in New Zealand is currently difficult, especially through the public health system, and considered that funding of DEN for patients who have already trialled stimulants (and have therefore already accessed specialist mental health services) would not address any treatment inequities.
- 10.10. The Committee also noted that the impacts of ADHD can extend beyond the health system (particularly within the justice system where Māori are significantly overrepresented, as is the prevalence of ADHD [[Young et al. Psychol Med. 2015;45:247-58](#)]), and any positive impacts from treatment may also have the potential for wider positive social impact.

Background

- 10.11. The Committee noted that an application for the funding of micronutrients (Hardy Nutritionals Daily Essential Nutrients [DEN] and/or EMPowerPlus Advanced [EMP+ Advanced]) for the treatment of ADHD was appraised by PTAC at its [May 2016 meeting](#), where it was recommended for decline.
- 10.12. The Committee noted that at that time, the application was for two unapproved products, with variation in product formulation even within trials. The Committee considered that at the time, the evidence provided was of weak strength but reasonable quality, with small participant numbers and open-label design. The Committee noted that since the 2016 consideration, additional trials have been published and that the applicants had included additional information regarding PTAC's previous concerns. The Committee also noted that the scope of this application had been narrowed.

Health Need

- 10.13. The Committee noted that ADHD is a disorder of both childhood and adulthood, and that severity is scalar and wide ranging, potentially leading to a wide array of issues for children, young adults, and their whānau. The Committee noted that recent changes to ADHD

diagnosis (either inattention or hyperactivity, as opposed to both) have led to an increased prevalence worldwide. The Committee noted that the prevalence of ADHD in New Zealand is widely believed to be approximately one in 20 children and one in 25 adults ([ADHD New Zealand](#)). The Committee noted that international prevalence ranges considerably, with prevalence reported anywhere from one in seven to 1 in 100.

- 10.14. The Committee noted that currently available treatment options for individuals with ADHD are the stimulants dexamfetamine and methylphenidate, and non-stimulant atomoxetine. The Committee noted that these agents are usually effective in treating individuals with ADHD and that they should not be prescribed without wrap-around care, though this commonly happens. The Committee noted that most trials providing evidence for efficacy of dexamfetamine, methylphenidate and atomoxetine were conducted with participants with ADHD with a tighter diagnosis than the DSM-5 criteria (ie inattention AND hyperactivity), and were provided wrap-around care. The Committee noted that for some people, stimulants do not provide an adequate effect, or are associated with intolerable side-effects. The Committee also noted that stimulant medications in children are associated with reduced growth.
- 10.15. The Committee noted that whānau of individuals with ADHD are also impacted, as people with ADHD can have more difficulty forming relationships and have worsened educational outcomes and workplace achievement. The Committee noted that clinical evidence does not suggest that stimulant medications improve these outcomes.
- 10.16. The Committee noted that the [New Zealand Health Survey 2018/19](#) reported that the prevalence of attention deficit and hyperactivity disorder (ADHD) in Māori children was 2.8% and that Māori children were not significantly more likely to have ADHD compared with non-Māori children (adjusted prevalence ratio 1.09; 95% CI 0.60 to 1.98). The Committee noted that access to specialist treatment through the public health system is difficult, with extremely long wait times, and considered that this greatly impacts equitable treatment access.

Health Benefit

- 10.17. The Committee noted that DEN is a broad-spectrum micronutrient supplement, with a suggested dosing regimen of up to 12-15 capsules per day. The Committee noted that at this dosage, DEN would be classified as a pharmaceutical because certain ingredients (eg vitamin D) would be administered in quantities commensurate with a prescription classification. The Committee also noted that there was some concern regarding the safety profile of consuming high levels of Vitamin A. The Committee considered that DEN should not be funded without Medsafe approval.
- 10.18. The Committee noted that the resubmission application for DEN for the treatment of ADHD specified that DEN be used after stimulants have been trialled and found to have an inadequate effect or intolerable side-effects. The Committee noted that this patient population would include individuals with moderate to severe ADHD who have already accessed or are currently accessing public or private mental health services.
- 10.19. The Committee noted a previously reviewed randomised controlled trial of micronutrients for the treatment of ADHD over eight weeks ([Rucklidge et al. Br J Psychiatry. 2014;204-306](#)). The Committee noted that 26% of participants in that trial had previously used stimulant medication, and that two different forms of micronutrients were used in the trial. The Committee considered at the time that this evidence to be of reasonable quality but weak strength, with limitations in trial design relating to low participant numbers.
- 10.20. The Committee noted the following studies published since the previous consideration of micronutrients for the treatment of ADHD in 2016:
 - 10.20.1. [Rucklidge et al. J Child Psychol Psychiatry. 2018;59:232-46](#): a double blind, randomised controlled trial of 93 children in New Zealand aged seven to 12 years who had been

medication free for four week prior to baseline assessment. Participants were treated with 15 capsules per day of micronutrients or placebo for 10 weeks. The overall Clinical Global Impression – Improvement (CGI-I) score had an effect size of 0.46 in favour of micronutrients. There was no effect on clinician or parent ratings for ADHD specific scores.

- 10.20.2. [Johnstone et al. J Am Acad Child Adolesc Psychiatry. 2022;61:647-61](#) with [erratum](#): a placebo-controlled randomised trial of 126 children in Canada aged six to 12 who had been medication free for at least two weeks prior to baseline assessment. Participants were treated with three to four capsules of either DEN or placebo three times daily for eight weeks. Both treatment arms showed an improvement in overall ADHD symptoms, but the DEN group had a greater overall percentage improvement on the CGI-I scale compared to placebo (54% versus 18%; risk ratio 2.97; 97.5% CI 1.5 to 5.9; $p < 0.001$).
- 10.20.3. [Darling et al. J Child Adolesc Psychopharmacol. 2019;29:688-704](#): a 1-year follow-up of Rucklidge et al (2018). Outcome was considered based on dominant therapy at 52 weeks (trial micronutrients [$n = 19$], medications [$n = 21$], and no treatment [$n = 35$]). 84% of those who continued micronutrient treatment were identified as "Much" or "Very Much" improved overall relative to baseline functioning (CGI-I), compared to 50% of those who switched to psychiatric medications and 21% of those who discontinued treatment ($p < 0.001$). The micronutrient group displayed better outcomes on measures of parent-rated hyperactivity and anxiety, and clinician-rated general function and mood (between-group effect sizes micronutrients vs. medication effect size = 0.73-1.01; micronutrients vs. no treatment effect size = 0.54-1.01). The most common reason for cessation of micronutrient treatment was cost and the number of tablets required. There were no novel or continued adverse events associated with treatment with micronutrients.
- 10.21. The Committee also noted the following studies related to micronutrients for the treatment of ADHD in children and adults:
- [Kaplan et al. J Child Adolesc Psychopharmacol. 2004;14:115-22](#)
 - [Rucklidge JJ. Harrison R. CNS Spectr. 2010;15:289-95](#)
 - [Rucklidge et al. J Atten Disord. 2011;15:79-91](#)
 - [Rucklidge et al. Prog Neuropsychopharmacol Biol Psychiatry. 2014;50:163-71](#)
 - [Gordon et al. J Child Adolesc Psychopharmacol. 2015;25:783-98](#)
 - [Rucklidge et al. J Atten Disord. 2017;21:522-32](#)
 - [Rucklidge et al. J Altern Complement Med. 2019;25:613-22](#)
 - [Johnstone et al. Nutrients. 2020;12:3394](#)
- 10.22. The Committee were also made aware of a comparative study of micronutrients versus methylphenidate in 20 children diagnosed with ADHD ([Harding et al. Altern Med Rev. 2003;8:319-30](#)). The Committee noted that patients in both groups experienced statistically significant improvements in the majority of scales tested.
- 10.23. The Committee considered that overall, the trials were of moderate strength and quality, that the three primary randomised controlled trials did not fully align to the requested clinically indicated group and considered that it was important that the New Zealand population was studied. The Committee noted that treatment with DEN showed an overall improvement in CGI scores which were maintained out to one year, but that there was mixed evidence relating to ADHD specific improvements. The Committee noted that there were no side effects reported out to one year of treatment with high doses of micronutrients but considered that longer follow-up would be needed to truly evaluate this.

- 10.24. The Committee considered that DEN would be best placed in the treatment paradigm post stimulants as that is where the greatest unmet health need exists.
- 10.25. The Committee noted a number of personal testimonials submitted with the application, many describing lived experience of people with ADHD in New Zealand and the high positive impact with DEN. The Committee noted that cost was reported as a large barrier to individuals with ADHD and their families accessing DEN.

Suitability

- 10.26. The Committee noted that people would be required to ingest up to 15 DEN tablets over three divided doses a day and considered that this may be challenging for some, especially children, however acknowledged the applicant's noting that special cups and training on pill swallowing are available, as well as an alternative powder form of DEN. The Committee noted that once a child was enrolled in the applicant's clinical research, it was reported that adherence to the three times daily dosing schedule was not an issue and considered this was evident in the trial results.
- 10.27. The Committee noted that the Darling et al. (2018) trial recruited only 93 of the target 100 participants for their study and considered that this may indicate that DEN may not be a popular a treatment option amongst all patients who discontinue stimulant treatment.
- 10.28. The Committee noted that unlike stimulant medications, there is no risk of diversion (the transfer of any legally prescribed controlled substance from the individual for whom it was prescribed to another person for any illicit use) with DEN.
- 10.29. The Committee noted that the size of the eligible population for DEN was growing due to increases in the prevalence of diagnosed ADHD over time. The Committee considered that data on the number of people who have trialled funded stimulants and atomoxetine could provide a reasonable estimate of this population.
- 10.30. The Committee noted that although patients in the requested indication would have already been diagnosed with ADHD, regular review is important as approximately 2% of patients become asymptomatic annually. The Committee therefore considered that diagnosis should be re-confirmed by a specialist prior to commencement of treatment with DEN and at the point of renewal. The Committee considered that following confirmation of diagnosis, treatment with DEN could be managed at the primary care level, which is especially beneficial within the context of the lack of available secondary care support.

Costs and Savings

- 10.31. The Committee considered it was reasonable to assume an uptake rate of 60% for DEN among the eligible population due to the health need associated with ADHD that cannot be managed adequately with currently funded medications, as well as a range of factors that may affect peoples' willingness to trial DEN including the large number of daily capsules. The Committee considered that the relatively small participation among the trials of DEN conducted in New Zealand were indicative of likely uptake patterns of DEN in a local context.
- 10.32. The Committee considered that there was no published or anecdotal evidence to suggest that treatment of ADHD with DEN would impact rates of inpatient hospitalisation.

Summary for assessment

- 10.33. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for DEN if it were to be funded in New Zealand for the treatment of ADHD. 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	Individuals with diagnosed ADHD who have not experienced an effective response or have experienced unacceptable side effects from optimal treatment with atomoxetine and methylphenidate hydrochloride or dexamphetamine.
Intervention	DEN capsules <ul style="list-style-type: none"> • Recommended dosage is 12 to 15 capsules per day.
Comparator(s)	Psychosocial support (eg. Webster-Stratton therapy)
Outcome(s)	<p><i>Adults (aged 16 years and older)</i></p> <p>Improved Clinical Global Impression score</p> <ul style="list-style-type: none"> • Rucklidge et al. Br J Psychiatry. 2014;204:306-15 reported that DEN therapy was associated with improved CGI-I scores compared to placebo (mean difference -0.71; 95% CI -0.16 to -1.27), adults children with ADHD. • Lloyd et al. Patient 2011;4: 247-57 reported that improved CGI-I scores were associated with health-related quality of life, among people with ADHD. <p><i>Children (aged 7 to 12 years)</i></p> <p>Improved Clinical Global Impression score</p> <ul style="list-style-type: none"> • Rucklidge et al. J Child Psychol Psychiatry. 2018;59:232-46 reported that DEN therapy was associated with improved CGI-I scores compared to placebo (mean difference -0.47; 95% CI -0.05 to -0.90), among children with ADHD. • Lloyd et al. Patient 2011;4: 247-57 reported that improved CGI-I scores were associated with health-related quality of life, among people with ADHD
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. Fomepizole for methanol poisoning

Application

- 11.1. The Committee considered fomepizole for methanol and/or ethylene glycol poisoning, in light of the following new information:
- New Zealand National Poisons Centre Antidote Stocking Guideline for Hospital Pharmacies for the Treatment of Poisoning Emergencies (DRAFT June 2022)
 - New published evidence for fomepizole in this indication
 - Letters of support for funding fomepizole from the New Zealand National Poisons Centre, the New Zealand ICU Network and the Australasian College of Emergency Medicine which were received in response to Pharmac's proposal to decline fomepizole.
- 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 fomepizole be funded with a **high priority**, subject to Special Authority criteria.

FOMEPIZOLE

Initiation

All of the following:

1. Either:
 - 1.1. Patient has a serum ethylene glycol or methanol concentration of greater than 20 mg/dL; or
 - 1.2. Either:
 - 1.2.1. Patient has a documented recent history of ethylene glycol or methanol ingestion with increased osmolal gap of greater than 10 mOsm/kgH₂O; or
 - 1.2.2. Both:
 - 1.2.2.1. Patient has a history of ethylene glycol or methanol ingestion; and
 - 1.2.2.2. At least two of the following:
 - 1.2.2.2.1. Arterial pH of less than 7.3; or
 - 1.2.2.2.2. Serum bicarbonate of less than 20 mmol/L; or
 - 1.2.2.2.3. Osmolal gap of greater than 10 mOsm/kgH₂O; or
 - 1.2.2.2.4. Urinary oxalate crystals present (only in ethylene glycol poisoning cases); and
2. Treatment with fomepizole will continue until the patient's methanol or ethylene glycol concentration is reduced below 20 mg/dL, symptoms have resolved, and pH has normalised.

11.4. In making this recommendation, the Committee considered the evidence for the health benefits of fomepizole and the suitability of fomepizole, especially for use in remote and rural areas.

Discussion

Māori impact

11.5. The Committee noted that there was limited evidence regarding the impact of methanol and/or ethylene glycol poisoning on Māori, however, considered that no evidence was identified to indicate it affects Māori more than any other population group.

Background

- 11.6. The Committee noted that PTAC considered fomepizole for this indication in [May 2019](#) and recommended it be funded with a high priority. Although the evidence base for the use of fomepizole in the treatment of ethylene glycol or methanol poisoning was poor, PTAC considered there is a high health need in patients with this condition; and the different adverse event profile of fomepizole compared to ethanol may reduce health sector costs in the treatment of these patients. PTAC considered that the priority of its recommendation should be reviewed if fomepizole would not reduce health sector costs.
- 11.7. Subsequently in [November 2019](#), PTAC had noted that specialist clinical advice obtained by Pharmac staff indicated that, while there may be benefits from the use of fomepizole compared with ethanol given its relative ease of administration, it was considered unlikely there would be any substantive reduction in health resource requirements and that shelf stock may expire before use. At that time, PTAC recommended that fomepizole in the treatment of ethylene glycol or methanol poisoning be funded only if cost-neutral to the health sector, as funding fomepizole would not result in a significant reduction of health sector costs at the pricing currently being sought by the supplier.
- 11.8. The Committee noted that this application was not able to progress based on cost-neutrality to the health sector due to the cost of fomepizole and concerns about levels of stock, and that in [June 2021](#), Pharmac included fomepizole in a proposal to decline inactive funding applications. Several letters of support for the funding of fomepizole were received by Pharmac in response to the proposal, including recently published data in relation to fomepizole compared with ethanol for the treatment of ethylene glycol poisoning.
- 11.9. In [March 2022](#), Pharmac decided not to progress the application for fomepizole for methanol poisoning to a decline decision, noting feedback that this application should remain open to be considered for funding due to the benefits above current treatment, the development of New Zealand antidote guidelines, and the inclusion of fomepizole on the WHO essential medicines list.
- 11.10. The Committee noted that Pharmac staff sought PTAC's views of the new evidence and likely usage of fomepizole according to the antidote stocking guideline.

Need

- 11.11. The Committee noted the health need of people with methanol and/or ethylene glycol poisoning has been discussed previously, including the fact that it is challenging to treat patients with poisoning in rural areas with an ethanol infusion. The Committee noted that there was limited evidence regarding the impact of methanol and/or ethylene glycol poisoning on Māori, however, considered that no evidence was identified to indicate it affects Māori more than any other population group.
- 11.12. The Committee noted that methanol poisoning is increasingly rare as methylated spirits no longer contains methanol. The Committee considered that case numbers per year, if available, would more accurately estimate annual methanol and/or ethylene glycol poisoning incidence, and considered this would be much fewer than the numbers of calls made to the National Poisons Centre about methylated spirits ingestion (estimated 60-80 calls per year related to methylated spirits, the majority of cases being ingestion with 40% occurring in those zero to three years of age).

Health Benefits

- 11.13. The Committee noted the new evidence from a systematic review and analysis that aimed to identify predictors of alcohol dehydrogenase inhibitor failure in 411 cases in subjects of all ages and comorbidities with ethylene glycol poisoning who received treatment with ethanol and/or fomepizole without extracorporeal treatment ([Beaulieu et al. Clin Toxicol \(Phila\). 2022;60:784-97](#)). The Committee noted that ethanol monotherapy was used in 180 events (1 case per patient n=165), fomepizole monotherapy in 231 events (1 case per patient n=168) and that there was ethanol co-ingestion in about one third of patients.
- 11.13.1. The Committee noted that treatment failure (defined as mortality, worsening of acid-base status, extracorporeal treatments used as rescue, or a worsening of kidney or neurological function after alcohol dehydrogenase inhibition was initiated) occurred in 16.7% with ethanol alone and in 8.7% fomepizole. The Committee noted that patients receiving ethanol alone had a more acidotic pH than those who received fomepizole (6.96 vs 7.20, respectively), that there was a longer time to presentation in those treated with ethanol alone than with fomepizole (six vs three hours), and that the time from presentation to receiving antidote was longer with ethanol alone than with fomepizole (ten vs three and a half hours). Members noted that studies including patients treated with ethanol were generally older than studies of patients treated with fomepizole, and considered that recent improvements in standard of care may have had some influence on improved patient outcomes in more recent studies.
- 11.13.2. The Committee noted that the median length of stay was four days with ethanol alone and 3 with fomepizole, and that death was reported in 9.4% with ethanol alone and 1.3% with fomepizole. The Committee note that acute kidney injury occurred in 14.0% with ethanol alone and 5.1% with fomepizole, that neurological worsening occurred in 15.8% with ethanol alone and in 2.8% with fomepizole, and that one case of anaphylaxis to fomepizole was reported.
- 11.14. The Committee noted an analysis of fomepizole elimination in a series of poisoned patients and healthy humans aged ≥ 12 years who were enrolled in the clinical trials of the use of fomepizole for methanol (n=11) and ethylene glycol (n=15) poisoning ([McMartin et al. J Med Toxicol. 2022;18:19-29](#)). The Committee noted that elimination of fomepizole was assessed after individual doses, both during and without intermittent haemodialysis; after repeated doses of fomepizole in methanol- and ethylene glycol-poisoned patients, the minimum trough concentration averaged 86–109 $\mu\text{mol/L}$, which was 10 times higher than the minimum therapeutic concentration.
- 11.15. The Committee was made aware of two systematic reviews of fomepizole compared to ethanol that did not establish superiority of fomepizole over ethanol in treatment of cases of ethylene glycol poisoning, although the reviews did not investigate these treatments for

methanol poisoning ([Druteika et al. Pharmacotherapy. 2002;22:365-72](#); [Wallman et al. Emerg Med J. 2002;19:431-2](#)).

- 11.16. The Committee considered that the new data did not substantially change its appraisal of the evidence for fomepizole. The Committee considered that no study was designed to compare the efficacy of the two treatments, and that the evidence was heterogenous, confounded by other factors, and subject to biases (eg missing data and publication bias). However, the Committee considered that higher quality evidence would not be expected to eventuate and considered that the available evidence supported use of fomepizole with reported efficacy at least equivalent to that of ethanol. The Committee noted that there is no evidence that fomepizole would reduce patient time in intensive care units (ICU) or reduce the need for dialysis. The Committee considered that the ease of fomepizole administration and its reduced adverse event profile compared to ethanol were the most relevant outcomes for Pharmac assessment. The Committee considered that it was reasonable to align with international guidance documents that reflect use of fomepizole as international best practice for this indication given the evidence base.

Suitability

- 11.17. The Committee noted the shelf life of fomepizole is 60 months and considered that its ease of administration would enable treatment to be initiated in smaller centres, although patients would be expected to require admission to ICU even if fomepizole were used. The Committee noted that fomepizole has treatment delivery benefits over ethanol and a potential benefit for rural patients via increasing equity of access to care.

Costs and Savings

- 11.18. The Committee considered that fomepizole would be stocked in all Emergency Departments and in remote rural clinics, however, it was difficult to determine likely total stock levels, usage and wastage (ie. due to expiry of most stock before use) across the country. The Committee considered that the risk of slippage was small as fomepizole is unlikely to be used in paracetamol overdoses (most cases being mild and associated with a low incidence of consequent liver toxicity).
- 11.19. The Committee noted the significant cost of ethanol treatment for methylene glycol or ethanol poisoning, however, considered that its view had not changed regarding the potential savings with fomepizole from a reduction in health resource requirements being unlikely. The Committee also noted that other generic forms of fomepizole are available, potentially providing opportunity for different price options for this medicine.
- 11.20. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for fomepizole if it were to be funded in New Zealand for methanol or ethylene glycol poisoning. 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	The patient population is limited to those who have ingested methanol or ethylene glycol.
Intervention	Fomepizole intravenous infusions. A loading dose of 15 mg/kg should be administered, followed by doses of 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours thereafter until ethylene glycol or methanol concentrations are undetectable or have been reduced below 20 mg/dL reduction of methanol or ethylene glycol. Majority of patients complete treatment in 72-96 hours.
Comparator(s)	Ethanol therapy, given intravenously.
Outcome(s)	Easier for hospitals to administer and requires less monitoring. Fewer adverse effects compared to ethanol.
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.	