Record of the Neurological Subcommittee of PTAC Meeting held on 29 October 2021

Neurological Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2021.

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

The Neurological Subcommittee may:

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

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

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

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

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

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

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

TABLE OF CONTENTS

1. Attendance

Present

Giles Newton Howes
Brian Anderson
John Mottershead
Paul Timmings

Apologies:
John Fink
Mark Weatherall

2. The role of PTAC Subcommittees and records of meetings

2.1. This meeting record of the Neurological Subcommittee of PTAC is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2021, available on the Pharmac website at https://pharmac.govt.nz/about/expert-advice/specialist-advisory-committees/specialist-advisory-committee-terms-of-reference/.

2.2. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Subcommittees and PTAC.

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

2.4. The Neurological Subcommittee is a Subcommittee of PTAC. The Neurological Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. The Neurological Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for treatments for Neurology that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for Neurology that differ from the Neurological Subcommittee's, or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'.

Pharmac considers the recommendations provided by both the Neurological Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for Neurology.

3. Phenobarbitone

Discussion

3.1. The Subcommittee noted that Pharmac was seeking advice following the announcement that the pharmaceutical supplier, API Consumer Brands is withdrawing from the New Zealand market, resulting in the discontinuation of its brand of phenobarbitone tablets. The Subcommittee noted that API's withdrawal from NZ is related to the tablet presentation of phenobarbitone only and was not anticipated to impact the supply of injection or powder phenobarbitone presentations.

3.2. The Subcommittee noted that phenobarbitone is listed as a WHO essential medicine. The Subcommittee noted that phenobarbitone is classified in the UK as a Category 1 epilepsy medicine, with the advice that patients be maintained on a specific brand. The Subcommittee noted that due to API shutting down its manufacturing plant, if a phenobarbitone product can be procured, it will be a different manufactured product meaning patients would need to undergo a change in brand.

3.3. The Subcommittee noted that in addition to its approved use in certain types of epilepsy, phenobarbitone tablets may be used, less commonly, for a range of indications including anxiety, trouble sleeping, drug withdrawal/ neonatal abstinence, palliative care, assisted death, cyclic vomiting syndrome, premedication, and sedation. The Subcommittee considered that there were appropriate funded alternatives for these indications.

3.4. The Subcommittee noted that around 500 people have been dispensed phenobarbitone tablets within the last year, most commonly in those aged 40+ years and that very few patients were initiated on phenobarbitone each year. The Subcommittee noted that the majority of phenobarbitone tablets are dispensed in the community and prescribed by GPs.

3.5. Members considered that a large cohort of patients with epilepsy were initiated on phenobarbitone when there were fewer agents available worldwide and that they have been maintained on treatment subsequently; however that there is now a large range of funded anti-epilepsy medicines which would meet their health need if phenobarbitone were no longer available.

3.6. Members noted that while it is now uncommon for patients with epilepsy to be initiated on phenobarbitone, it may be occasionally trialled in patients with refractory seizures, for example as a fourth-line treatment option. Members considered that alternative, newer agents could be used in these instances, however some of the agents (eg. zonisamide) are not currently listed on the Pharmaceutical Schedule. The Subcommittee considered that while there was a preference for the continued availability of phenobarbitone tablets for new patients, this is a small patient group that may be appropriately managed with other agents.

3.7. The Subcommittee noted the possible withdrawal symptoms of ceasing phenobarbitone (particularly when discontinued in a short period of time) and that people taking phenobarbitone only remain on treatment becuase it is effective for them. The Subcommittee therefore considered that it was important that phenobarbitone tablets remain available for ongoing use.

3.8. Members considered that if phenobarbitone tablets were no longer available, alternative medicines could reasonably be trialled including primidone. Members noted that complete treatment changes for people with epilepsy have a number of complexities and different tolerability profiles to be considered.

3.9. The Subcommittee considered that if only an unapproved phenobarbitone tablet presentation could be obtained following the discontinuation of the API brand, while this would be preferable to no product, there is both increased administrative burden, but also the potential for increased patient anxiety about a change.

3.10. Similarly, the Subcommittee considered that if only one tablet strength were available, while there would be an increased risk of dosing errors and a requirement for appropriate educational support, this scenario would be preferable to no phenobarbitone tablet availability.

3.11. The Subcommittee considered if phenobarbitone tablets were no longer available, alternative anti-epilepsy medicines could be trialled, namely primidone. Members noted that it might be possible to reconstitute an intravenous formulation as an oral medicant for children, but such practice would be subject to conditions the same as a brand change. Members considered that with a medicine change this would typically involve mandatory driving cessation for at least six months even if the person did not experience seizures with the change.

3.12. The Subcommittee considered that Pharmac could seek further advice from relevant healthcare professionals regarding the use of phenobarbitone tablets in palliative care, although noted that the powder and injection presentations would not be impacted by the API discontinuation.

Implementation for a change in brand

3.13. The Subcommittee noted that as a Category One epilepsy medicine, any change in brand would need to be carefully monitored for change in therapeutic effect. Members were not aware of any international guidelines relating to managing a change of phenobarbitone brand.

3.14. The Subcommittee considered that a brand change for phenobarbitone could managed at GP level. Members considered that GPs treating patients with epilepsy may wish to discuss a phenobarbitone brand change with a local neurologist; however this was not necessarily required for the management of the brand change. This consideration by the Subcommittee was predicated however on good, timely advice being made available to prescribers. The Subcommittee also considered that it would be useful for Pharmac to make clinical advisers available, where appropriate, to local neurologists to help support this brand change.

3.15. The Subcommittee noted that serum phenobarbital serum concentrations can be monitored with blood testing. The Subcommittee considered that for epilepsy patients, monitoring of phenobarbital concentration would be important during a phenobarbitone brand change. The Subcommittee considered that this could be adequately managed at a primary care level.

3.16. Members noted that the purpose of monitoring serum phenobarbital would be to check whether concentrations are maintained at the same level pre- and post-brand change. The Subcommittee noted that the aim of measuring baseline phenobarbital concentrations was to ensure continuity of phenobarbitone

therapeutic effect, where on occasion, phenobarbitone may still be providing good therapeutic effect even when outside the target therapeutic range. The Subcommittee considered that maintenance of baseline (pre-brand change) serum phenobarbital concentration could be considered stable at plus or minus (+/-) 10%.

3.17. Members discussed whether a wider range would be appropriate (eg. +/-20%) given intra-person variation, however considered, given the narrow therapeutic index for phenobarbitone, +/- 10% was the most appropriate guideline for bioequivalence.

3.18. The Subcommittee recommended that four serum tests be performed, namely:

- approximately three weeks pre-brand change [baseline 1],
- within the week before the change [baseline 2],
- within the first week following a brand change (ideally 4-10 days after the first dose of the new brand), and
- at one month post-brand change.

3.19. The Subcommittee considered two baseline phenobarbital concentrations were required to establish more accurate baselines (given normal day-to-day variability in phenobarbital levels), and considered that if there was appreciable variation between baseline 1 and baseline 2 levels that this would suggest instability and necessitate closer post-change serum monitoring (with more testing especially early in the change). All phenobarbital concentrations should be obtained as trough samples, ie pre-dose.

3.20. The Subcommittee noted that different laboratories may quote slightly different therapeutic ranges, and therefore in the interest of clarity it would be important that each test for an individual should be processed by the same laboratory for that individual.

3.21. The Subcommittee considered that there would be at least an extra two GP visits required for epilepsy patients if there was a brand change for phenobarbitone, to support phenobarbital monitoring - one before and one after any brand change.

3.22. The Subcommittee noted that, as with any medicine, the target therapeutic range for phenobarbital is an epidemiological construct based on group (average) effects, where on a statistical basis, a few individuals' responses would be expected to differ and lie outside that range, and as such, some patients will have effective clinical outcomes with phenobarbitone, but with phenobarbital concentrations outside of this range. The Subcommittee reiterated that some people treated with phenobarbitone will have what could be formally considered 'sub-therapeutic' phenobarbital concentrations but nonetheless be well managed with clinically effective and appropriate doses of phenobarbitone, despite being less than the lower limit of the formal therapeutic range for phenobarbital. The Subcommittee therefore considered that if there was a brand change for phenobarbitone, phenobarbital concentrations should be maintained pre- and post-brand change, and prescribers should not increase phenobarbitone dosages in order to simply reach the lower limits of that phenobarbital target therapeutic range unless there was clinical need for dose change.

3.23. The Subcommittee noted that if a patient's phenobarbital concentrations were outside of the recommended range, that GPs may wish to contact a local neurologist for advice.

3.24. The Subcommittee noted that side effects of increased phenobarbital levels include headache, mood changes, drowsiness and sedation, while reduced phenobarbital levels may result in reports of sleep difficulties or insufficient clinical effect (including seizure activity).

3.25. Members considered that if a patient was unwilling or unable to have serum monitoring that the treating clinician should determine what a bioequivalent response would be for that patient.

3.26. The Subcommittee considered that there was a body of international literature of transitioning epilepsy medicines over a three-month period and considered that any changes to phenobarbitone tablets should be managed over a period of at least three months. Members considered that if bioequivalence between brands was established, there would be no reason to not have an immediate change of brands (rather than a cross titration of the outgoing and incoming brands). The Subcommittee considered that cross titrating the two brands would extend the time period for serum monitoring which may be less favourable, particularly if being used to assess fitness to drive. Members noted that people would likely be anxious about a change and a transition would need to be appropriately planned with the patient and their health care professional.

3.27. The Subcommittee noted that if prior to the brand change, a patient's epilepsy is not well controlled, this may be a good opportunity for their clinical management to be reviewed.

3.28. The Subcommittee noted that Pharmac had received feedback from Waka Kotahi (NZ Transport Agency) regarding a different anti-epilpesy medicine (primidone) that determining medical fitness to drive is the responsibility of the Health Practitioner. Members confirmed this advice that the decision regarding fitness to drive was that of the treating clinician on a patient-to-patient basis. Members noted that if a change in medicine, rather than a change in brand was undertaken, that the six-month driving stand down would apply as per standard procedure.

3.29. Members considered that while it was important that anyone taking phenobarbitone engage with their GP, a change would require a health care professional team. It is important that other health care professionals, including practice nurses and pharmacists understand the potential issues with a phenobarbitone brand change and reasoning for phenobarbital monitoring to ensure that patients are appropriately and accurately counselled throughout their brand change journey.

4. Rufinamide – Lennox-Gastaut Syndrome

Application

4.1. Text The Subcommittee reviewed an application from Eisai New Zealand Ltd for rufinamide as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 4 years of age and older.

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

Recommendation

4.3. The Subcommittee **recommended** that rufinamide be funded as adjunctive therapy in the treatment of seizures associated with LGS with a **high priority,** within the context of neurology treatments, subject to the following Special Authority criteria:

RUFINAMIDE
Initial application from a neurologist or paediatric neurologist, or on the recommendation of a neurologist or paediatric neurologist . Approvals valid for 15 months.
All of the following:

1. Patient has Lennox-Gastaut Syndrome; and
2. Seizures are not adequately controlled by, or patient has experienced unacceptable side effects from, optimal treatment with sodium valproate and at least two other anti-epileptic drugs; and
3. Rufinamide will be used as adjunctive treatment.

Renewal from neurologist or paediatric neurologist, or on the recommendation of a neurologist or paediatric neurologist. Approvals valid for 24 months.
All of the following:

1. The patient has demonstrated a significant and sustained improvement in seizure rate or severity and/or quality of life compared with that prior to starting rufinamide treatment.

4.4. In making this recommendation, the Subcommittee considered:

- the high health need of the relatively small group of people with LGS
- the high family/whānau burden of care due to the impact of the condition
- the strong, high-quality evidence of benefit from rufinamide in terms of reducing "tonic-atonic" seizures ("drop attacks"), particularly noting the low incidence of LGS
- that a reduction in "tonic-atonic" seizures was a clinically important outcome that could reduce hospitalisations and would likely have a positive impact on a patient's family/whānau; although the Subcommittee recognised that the parental satisfaction survey results were of poor quality and that there was no published evidence identified to support a reduction in hospitalisations with rufinamide.

Discussion

4.5. The Subcommittee noted that LGS is a severe developmental encephalopathy with onset in early childhood (usually before eight years of age) that is characterised by intractable, multiple, generalised seizure types, and accounts for approximately 1-10% of childhood epilepsies (Camfield. Epilepsia. 2011;52:3-9). The Subcommittee noted that LGS is a distinct group compared to medically refractory epilepsy, that LGS can develop from West syndrome, and that severe presentations of LGS can include developmental and epileptic encephalopathy. The Subcommittee noted that patients with LGS may experience a large number of seizures daily (eg up to 30 seizures per day), including many generalised tonic-clonic seizures.

4.6. The Subcommittee noted that there is a significant health need for patients as well as their family and whānau as a result of LGS. The Subcommittee noted that, in September 2020 when PTAC considered zonisamide for treatment refractory epilepsy, PTAC had considered that any appreciable decrease in seizure frequency or severity would have major benefits for patients as well as their caregivers/family/whānau by reducing the family burden of care, depression and anxiety, and may improve the caregiver/family/whānau ability to work. The Subcommittee considered that LGS has higher healthcare costs compared to other childhood epilepsies, the greatest costs being attributable to inpatient care, home nursing care, and medication (Strzelczyk et al. Epilepsy Behav. 2021;115:107674).

4.7. The Subcommittee noted that while there have been no specific data identified for Māori with LGS, Māori patients have worse health outcomes compared with non-Māori with epilepsy in New Zealand. The Subcommittee noted that Māori are less likely to be treated (P=0.024) and have a higher mortality rate (hazard ratio = 1.41, 95% CI=1.08-1.83) (Hamilton Epilepsia 2020;61:519-29). The Subcommittee also considered that Pacific peoples are more likely to present in hospital with a seizure lasting more than 10 minutes; 29.31 per 100,000 and 26.55 per 100,000 respectively compared with 19.13 per 100,000 in Europeans, adjusted for age (Bergin Epilepsia 2019;60:1552-64).

4.8. The Subcommittee considered that an estimate of 80 patients in New Zealand with LGS receiving insufficient benefit from funded treatments is low and considered the actual number to be higher, with a maximum of 200 patients.

4.9. The Subcommittee noted that the supplier described the current treatment paradigm for LGS in New Zealand as involving treatment with a first-line anti-epileptic drug (sodium valproate), followed by initiation of a second-line anti-epilepsy drug (AED), then further specialist care. However, the Subcommittee considered that many patients with LGS would already be under the care of a specialist by the time a diagnosis of LGS was made (eg due to having West syndrome initially). The Subcommittee noted that other non-pharmacological treatment options include surgery and ketogenic diets; however, the Subcommittee considered that these are not commonly and consistently available for LGS in New Zealand.

4.10. The Subcommittee considered that the aim of treatment for LGS is to reduce the rate of disabling seizures including tonic and atonic seizures (“drop attacks”). Members noted that seizure control in developing children was also particularly important. The Subcommittee noted that most disease-related morbidity in LGS is due to falls secondary to tonic or atonic seizures which result in increased health resource use such as Accident & Emergency visits and hospitalisations. The Subcommittee considered that patients with LGS rarely receive freedom from seizures despite the use of all current funded treatments.

4.11. The Subcommittee noted that rufinamide is a carboxamide derivative that modulates the activity of sodium channels, prolonging their inactive state. The Subcommittee noted that rufinamide is Medsafe approved as adjunctive therapy in the treatment of seizures associated with LGS in patients four years of age and older. The Subcommittee noted that rufinamide should be taken twice daily in two equally divided doses, and that the recommended dosing depends on patient age, weight, and whether there is concurrent treatment with sodium valproate (due to the interaction between the two agents). The Subcommittee noted that rufinamide

has a range of suitable presentations (including oral suspension), can be dissolved, and can be administered via nasogastric tube.

4.12. The Subcommittee noted that the supplier has proposed that rufinamide be used for the fourth-line adjuvant treatment of LGS, in place of specialist care, however, the Subcommittee considered that most children with LGS would already be under the care of a paediatric neurologist at this stage in their treatment.

4.13. The Subcommittee noted that the key clinical evidence for adjunctive rufinamide in the treatment of LGS came from two key clinical trials, Study 022 and Study 304.

4.14. The Subcommittee noted that Study 022 was a multicentre, randomised, double-blind, placebo-controlled phase III study which investigated rufinamide plus a standard AED regimen compared with placebo plus a standard AED regimen in 138 patients with LGS (Glauser et al. Neurology. 2008;70:1950-8). The Subcommittee noted that participants were aged four to 30 years with a history of multiple seizure types, ≥90 seizures in the previous month, were receiving a fixed-dose regimen of one to three AEDs and had bodyweight ≥18kg.

4.14.1. The Subcommittee noted that, after a duration of 12 weeks (two weeks titration and 10 weeks maintenance), the median reduction in total seizure frequency per 28 days was 32.7% in the rufinamide group vs 11.7% in the placebo group (P=0.0015). The improvement in seizure severity was 53.4% in the rufinamide group vs 30.6% in the placebo group (P=0.0041). The Subcommittee noted that the median decrease in "tonic–atonic" seizure frequency (tonic seizures and atonic seizures defined as "tonic-atonic" seizures) per 28 days relative to baseline was a decrease of 42.5% in the rufinamide group vs an increase of 1.4% in the placebo group (P<0.0001); the Subcommittee considered that this provided evidence for a clinically important benefit from rufinamide.

4.14.2. The Subcommittee noted that the parental satisfaction survey reported no significant difference between the two groups in mean composite score, and all individual items were similar (P>0.2) except for seizure severity which reported an improvement in the rufinamide group vs the placebo group (P=0.0041). The Subcommittee considered that the outcomes used in the parental satisfaction survey did not necessarily translate into the 'real world' impacts which would be expected from effective treatment. Members considered that parent and caregiver satisfaction would likely be achieved in a number of cases in the real world, particularly in relation to carer burden related to drop attacks.

4.14.3. The Subcommittee also noted that the common adverse events (AEs) reported in Study 022 include vomiting and somnolence and that there were six patients, all in the rufinamide group, who withdrew from the study due to AEs. The Subcommittee considered that the short titration period (two weeks) may have contributed to the number of withdrawals.

4.15. The Subcommittee noted that Study 304, a multicentre, randomised (1:1), double-blind, placebo-controlled phase III study investigated the clinical benefit of rufinamide compared with placebo (with one to three concomitant AEDs allowed) in 59 patients. The Subcommittee noted that the participants were aged four to 30 years with LGS diagnosed based on seizure history and EEG pattern, with ≥90 seizures in the previous month, and bodyweight ≥15kg (Ohtsuka et al. Epilepsy Res. 2014;108:1627-36).

4.15.1. The Subcommittee noted that, after a duration of four-weeks baseline, two weeks titration, and 10-weeks maintenance, the median change in frequency of "tonic-atonic" seizures was −24.2% in the rufinamide group vs −3.3% in the placebo group (P=0.003). The Subcommittee noted that the median change in frequency of total seizures was −32.9% in the rufinamide group vs −3.1% in the placebo group (P< 0.001).

4.16. The Subcommittee noted the results of Study 305, an extension of Study 304 in 54 patients which investigated the clinical benefit of rufinamide (Ohtsuka et al. Epilepsy Res 2016;121:1–7). The median change in the frequency of tonic–atonic seizures (relative to double-blind study start) was −39.3% at 12 weeks, −40.6% at 24 weeks, −46.8% at 32 weeks, −47.6% at 40 weeks, and −36.1% at 52 weeks.

4.17. The Subcommittee noted the results of several other extension studies: Study 022, 022E, 303, 304 and 305 (Arzimanoglou et al. Neurology. 2018; 90 (15_suppl):P1.273). The median reduction in "tonic-atonic" seizure frequency in Study 022 was 42.5% in the rufinamide group (n=74) vs −1.4% in the placebo group (n=64; P<0.0001), and in Study 304 was 24.2% (n=29) and 3.3%, respectively (n=30; P=0.003). The median % reduction in total seizure frequency in Study 022 was 32.7% in the rufinamide group and 11.7% in the placebo group (P=0.0015), and Study 304 was 32.9% and 3.1%, respectively (P<0.001). The Subcommittee noted that participant age did not appear to affect rufinamide clearance and the clinical trial data indicated that rufinamide's pharmacokinetic profile was comparable across ages (from one year and older), with no dose adjustments required according to patient age.

4.18. The Subcommittee noted the evidence for rufinamide from post-hoc analyses, subgroup analyses, expert reviews, retrospective chart reviews, meta-analyses, Cochrane reviews, and conference abstracts that were provided by the supplier. The Subcommittee also noted the following evidence for rufinamide:

- Panebianco et al. Cochrane Database Syst Rev. 2020;11:CD011772
- Brigo et al. Cochrane Database Syst Rev. 2021;4:CD003277
- Sharawat et al. Seizure. 2021;91:296-307

4.19. The Subcommittee noted that the primary rufinamide trials were of relatively short duration given LGS is a lifelong condition and that the comparator treatments used in the trials were not entirely reflective of available treatments in New Zealand. However, on balance, the Subcommittee considered that the available evidence for rufinamide in LGS was strong and of high quality, particularly recognising the relatively low incidence of the condition. Members also noted that the continuation of rufinamide observed in the aforementioned trials, given the chronic nature of the condition was promising and suggested continued efficacy.

4.20. Members considered that the strength and quality of evidence for rufinamide in LGS was substantially better than that of a number of the agents currently used in New Zealand.

4.21. The Subcommittee considered that the reduction in "tonic-atonic" seizures was a clinically important outcome that could reduce hospitalisation consequent to "drop attacks". Members considered that this could reduce the impact of LGS on a patient's family/whānau, although the Subcommittee noted that the evidence for Quality of Life was of poor quality and there was no evidence identified to support

a reduction in hospital admissions for other reasons with rufinamide. This reduction in “tonic-atonic” seizures was speculated to translate into more home-based care for patients with LGS (as opposed to inpatient care within a hospital, institute or care home, which can be expensive). The Subcommittee considered there would not be a significant change in cost to the health sector in terms of monitoring. Members considered that reduced hospital care needs could result in savings to the health system and recommended that Pharmac include these relevant costs and savings in analysis.

4.22. The Subcommittee noted that the application proposed rufinamide be used as a third-line adjunctive treatment for LGS and considered that, as seizure freedom is unlikely to be attained in LGS, clinicians treating such patients would prescribe AEDs sequentially for adjunctive treatment. The Subcommittee considered that given the evidence for rufinamide is superior to that of other funded AEDs, it would be preferable to use it earlier ahead of treatments without proven efficacy. The Subcommittee considered the phenomenon that is the nature of the treatment paradigm, where a treatment used as a later line would be less effective than if given as an earlier line. The Subcommittee also considered rufinamide is unlikely to reduce the use of other AEDs when given after those drugs.

4.23. The Subcommittee considered that funding rufinamide would likely reduce healthcare costs related to seizure activity, including drop attacks and while this is important, considered that rufinamide is unlikely to reduce other use of health services because this is a population with high health needs due to debilitating chronic condition. Members noted that a reduced need for inpatient hospital care would be anticipated, so cost shift would likely occur. The Subcommittee agreed with supplier’s estimates of the adjunctive use of other AEDs if rufinamide were funded.

4.24. The Subcommittee considered that according to the discontinuation rates from Study 022e, only 17% of patients may remain on rufinamide at 60 months (Kluger et al. 2010). They also noted that Sharawat et al 2021 found much lower discontinuation rates of 10%, and considered the discontinuation would likely plateau at 2 years (Sharawat et al. Seizure. 2021;91:296-307). However, the Subcommittee considered that the retention of rufinamide treatment is likely to be greater in the real world compared to trials due to the nature of the condition and few available treatments.

4.25. The Subcommittee considered that the Special Authority criteria should allow funded access to rufinamide to those who have trialled three prior AEDs including sodium valproate. Additionally, the Subcommittee considered that Special Authority applications should be submitted by a neurologist or paediatric neurologist to ensure treatment is appropriately tailored to patients. The Subcommittee noted that LGS patients would be under the care of a specialist therefore do not anticipate any issues with this requirement.

4.26. The Subcommittee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for rufinamide if it were to be funded in New Zealand for LGS. 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 Subcommittee’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 Lennox-Gastaut Syndrome four years of age and older, whose seizures are not adequately controlled or have experienced unacceptable side effects from at least three prior AED treatments, including sodium valproate.
Intervention	Rufinamide as an adjunctive therapy, with other AEDs Initial rufinamide dose 400 mg a day, followed by incremental increases in dosage to the target maintenance dose, or a maximum maintenance dosage of up to 3200 mg per day. To be taken indefinitely if tolerated and efficacious.
Comparator(s) (NZ context)	Other AEDs • Sodium valproate • Lamotrigine • Topiramate • Clobazam • Levetiracetam
Outcome(s)	Reduction in "tonic-atonic" seizures ("Drop attacks")

Table definitions:

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

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

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

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

5. Perampanel - refractory epilepsy with partial-onset seizures and for refractory epilepsy with generalised seizures

Application

5.1. The Subcommittee noted that Pharmac had received the following applications for perampanel in the treatment of epilepsy:

- An application from Eisai New Zealand Ltd for the adjunctive ie additional add-on, treatment of partial-onset seizures (POS) with or without secondary generalised seizures in adult and adolescent patients from 12 years of age with epilepsy; and

- An application from Eisai New Zealand Ltd for the adjunctive (add-on) treatment of primary generalised tonic-clonic (PGTC) seizures in adult and adolescent patients from 12 years of age with idiopathic generalised epilepsy; and

- A clinician application for use of perampanel in refractory epilepsy, most commonly focal epilepsies but also in complex myoclonic epilepsies.

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

Background

5.3. The Subcommittee noted that PTAC considered the above perampanel applications at its February 2021 meeting, and at that time, PTAC recommended perampanel be funded for the following indications subject to Special Authority criteria:

- partial onset [focal] seizures (POS), with a medium priority
- primary generalised tonic-clonic (PGTC) seizures, with a low priority
- complex myoclonic epilepsy, with a low priority.

5.4. The Subcommittee noted that PTAC had considered that Pharmac should seek specialist advice regarding the applications for perampanel, especially regarding the following particular aspects:

- ascertaining where complex myoclonic epilepsy fits into the diagnostic and therapeutic pathway,
- the optimal positioning of perampanel within New Zealand treatment paradigms for epilepsies,
- appropriate dosing and stopping criteria for funded perampanel treatment,
- monitoring requirements for patients on perampanel treatment, and
- proposed Special Authority criteria.

Discussion

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

5.6. The Subcommittee noted that perampanel is a first-in-class AMPA glutamate receptor antagonist. The Subcommittee noted that perampanel is an oral tablet taken once daily at night and is approved by Medsafe for the adjunctive treatment of adult and adolescent patients from 12 years of age with epilepsy who have either POS with or without secondary generalised seizures, or PGTC seizures in patients with idiopathic generalised epilepsy.

Primary generalised epilepsy

5.7. The Subcommittee noted that diagnostic terminology in epilepsy continues to evolve, resulting in differences in terminology within clinical practice and in clinical trials. This difficulty with the taxonomy of the disease can cause some confusion in describing types of epilepsy and seizures. The Subcommittee noted that generalised tonic-clonic convulsions may be focal onset (also known as secondarily generalised) or primarily generalised. The Subcommittee noted that childhood onset epilepsy syndromes often have generalised seizure types (absences, myoclonic seizures, and generalised tonic-clonic convulsions). The Subcommittee considered that the terms primary generalised epilepsy (PGE) or

idiopathic generalised epilepsy (IGE) would better to describe the patient groups referred to by PTAC and by the supplier applicant as experiencing PGTC seizures; members noted that this did not necessarily alter the size or characteristics of the patient population in question, rather, it more accurately described it.

5.8. The Subcommittee considered that people with PGE or IGE typically have childhood epilepsy that may continue into adulthood and many have a high health need. The Subcommittee considered that primary generalised seizure types may be worsened by some anti-epilepsy drugs (AEDs) therefore generally only sodium valproate, lamotrigine, levetiracetam and topiramate are used for their funded treatment - all of which have reported efficacy in treating people with generalised tonic-clonic (GTC) seizures. The Subcommittee noted that clobazam, clonazepam and ethosuximide may also have a role in some generalised seizure types.

5.9. The Subcommittee noted the evidence for perampanel in primary generalised epilepsy included the placebo-controlled Study 332 in 162 patients with IGE with PGTC seizures (French et al. Neurology.2015;85:950-7) and its open-label extension (Wechsler et al. Neurology. 2017;88 (16_Suppl) P5.233), an observational study (Villanueva et al. Epilepsia. 2018;59:1740-52) and a network analysis indirect comparison provided by the supplier (IMS Health, 2015), as described by PTAC in its February 2021 meeting record.

5.9.1. The Subcommittee noted there is evidence that people with refractory epilepsy receive lesser benefits from treatments used in later lines of therapy, and that rates of seizure freedom are low in later lines (Villanueva et al. 2018).

5.9.2. The Subcommittee noted that study 332 participants experienced a range of mutually inclusive seizures including myoclonic jerks in 40% of participants. The Subcommittee noted the authors reported the median change in PGTC seizure frequency from baseline was a 76.5% decrease with perampanel compared with a 38.4% decrease with placebo and considered that these outcomes were reasonable compared to outcomes reported for other AEDs eg levetiracetam.

5.9.3. The Subcommittee noted that the network analysis including six studies and provided an indirect comparison of PGTC seizure response (>50% reduction in PGTC seizure frequency), all seizure response (>50% reduction in all types of seizures frequency), PGTC seizure 75% response, PGTC seizure freedom, total seizure freedom and withdrawal due to adverse events. The Subcommittee considered the results suggested that perampanel had similar efficacy to topiramate and levetiracetam, although the 95% confidence intervals for the odds ratios for all outcomes crossed the line of significance (1) and therefore it was uncertain whether the outcomes favoured perampanel or the comparator. Members noted that perampanel was associated with higher withdrawals due to adverse events.

5.10. The Subcommittee considered that the proposed Special Authority criteria would target patients with GTC seizures and seizures of any type. The Subcommittee considered that referring to the target group as primary generalised epilepsy (instead of primary generalised tonic-clonic seizures) would effectively target the appropriate population and might only change patient numbers by a small amount without affecting uptake of perampanel significantly. Members considered that this amendment would also encompass the majority of the patients with complex

myoclonic epilepsy (CME); another group being considered for perampanel treatment. The Subcommittee otherwise agreed with the criteria recommended by PTAC for this group, and therefore considered the following Special Authority criteria would be appropriate for targeting funding to this group:

> **Initial application** – (primary generalised epilepsy). Application from any relevant practitioner. Approvals valid for 15 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has primary generalised epilepsy; and
> 2. Seizures are not adequately controlled by, treatment is contraindicated with, or patient has experienced unacceptable side effects from optimal treatment with all of the following: sodium valproate, topiramate, levetiracetam and lamotrigine.
>
> **Renewal** – (primary generalised epilepsy). Applications from any relevant practitioner. Approvals valid for 24 months for applications meeting the following criteria:
> 1. The patient has demonstrated a significant and sustained improvement in seizure rate or severity and/or quality of life compared with that prior to starting perampanel treatment.

Partial onset epilepsy

5.11. The Subcommittee noted that focal (partial) onset seizures are the most common seizure type, accounting for most adult-onset epilepsy. The Subcommittee considered that most AEDs are generally safe and offer benefits for people with POS, however, as some AEDs can be associated with a range of contraindications and side effects, it is important to provide funded access to a variety of AEDs for POS.

5.12. The Subcommittee noted evidence for perampanel in refractory POS from four clinical trials of similar design, including patients with epilepsy refractory to either more than two or 1-3 AEDs (French et al. Neurology. 2012;79:589-96; French et al. Epilepsia. 2013;54:117-25; Krauss et al. Neurology. 2012;78:1408- 15; Nishida et al. Acta Neurol Scand. 2018;137:392-99), from an extension study including participants from three of these clinical trials (Krauss et al. Epilepsia. 2013;54:126-34; Krauss et al. Epilepsia. 2014;55:1058-68; Krauss et al. Epilepsia. 2018;59:866-76), and from an indirect comparison with lacosamide provided by the supplier (unpublished).

5.12.1. The Subcommittee noted the extension study reported persistence of 39% at four years with freedom from seizures in about 12% of patients remaining on treatment. The Subcommittee considered that the indirect comparison suggested perampanel's efficacy was similar to that of lacosamide with regard to median change in seizure frequency, 50% response rates at 28 days and seizure freedom rates, although noted that the reported confidence intervals were wide.

5.13. The Subcommittee noted the Special Authority criteria proposed that patients with POS had trialed five AEDs (including sodium valproate, where indicated) before being eligible for perampanel and considered this was clinically appropriate. The Subcommittee considered that, based on the evidence of perampanel having similar efficacy as lacosamide, it would be appropriate for perampanel to sit alongside lacosamide in treatment paradigm for this group. However, the Subcommittee considered that perampanel could displace lacosamide (ie lacosamide could be used later in the paradigm) if perampanel provided this similar benefit at a lower cost. The Subcommittee considered there could be a desire to use perampanel as early as possible in the treatment of POS but considered that there was presently insufficient directly comparable evidence to inform the appropriateness of its earlier use. The Subcommittee considered that ongoing studies may help to inform relative efficacy of current and new treatments

(including perampanel) in future. Overall, the Subcommittee agreed with the Special Authority criteria proposed by PTAC for this group with POS as follows:

> **Initial application** – (partial-onset epilepsy). Application from any relevant practitioner. Approvals valid for 15 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has partial-onset epilepsy; and
> 2. Seizures are not adequately controlled by, treatment is contraindicated with, or patient has experienced unacceptable side effects from optimal treatment with all of the following: sodium valproate, topiramate, levetiracetam and any two of carbamazepine, lamotrigine and phenytoin sodium.
>
> **Renewal** – (partial-onset seizures). Applications from any relevant practitioner. Approvals valid for 24 months for applications meeting the following criteria:
> 1. The patient has demonstrated a significant and sustained improvement in seizure rate or severity and/or quality of life compared with that prior to starting perampanel treatment.

Complex myoclonic epilepsy

5.14. The Subcommittee noted that complex myoclonic epilepsy (CME) generally has onset in childhood and that the condition may include myoclonic jerks or myoclonic seizures which can be focal in onset (partial). The Subcommittee noted that CME is most often part of a generalised epilepsy, such as the following:

- Rare progressive myoclonic disorders such as Lafora disease and Unverricht–Lundborg disease (ULD) which are associated with other features, such as ataxia and intellectual disability
- More common epilepsy syndromes, such as Doose syndrome and Dravet's syndrome, where epilepsy is the key clinical issue although there may be associated intellectual disability
- Other epilepsy syndromes which have limited non-epilepsy features such as juvenile myoclonic epilepsy (JME), which is the most common.

5.15. The Subcommittee considered that patient numbers in CME are low, predominantly from LaFora disease and ULD, and noted Finnish data reflecting a population with high prevalence of ULD reported 1.5 cases of UL per 100,000 in the population (Sipila et al. Neurology. 2020;95:e3117-e3123). The Subcommittee considered that refractory JME was more common than ULD based on prevalence of 3 per 10,000 in a Norwegian population as reported by Syvertsen et al (Epilepsies. 2017;58:105-12). Overall, the Subcommittee considered that, based on the Finnish prevalence data, the group with rare epilepsies (including other myoclonic epilepsies) that are refractory to funded AEDs was small and would consist of approximately 300 people in New Zealand.

5.16. The Subcommittee considered that most patients with refractory JME and most patients with progressive myoclonic epilepsies would be within the group targeted by the supplier's PGTC definition. The Subcommittee noted that this differed from PTAC's view of where the patient group with complex myoclonic epilepsy fits relative to the supplier's proposed PGTC and POS groups. The Subcommittee considered that the reason for this difference was the nuanced and evolving nomenclature in epilepsy but confirmed that most patients with CME would be a subset of the patients with IGE/primary epilepsy with refractory epilepsy, and not a subset of the POS group. The Subcommittee considered that some patients with CME would not have experienced a major, generalised tonic clonic seizure but instead would experience frequent myoclonic jerks.

5.17. The Subcommittee considered that patients with CME generally receive the same current treatments as IGE / PGTC following the same treatment sequence (ie sodium valproate, topiramate, levetiracetam and lamotrigine). The Subcommittee noted that some sodium channel blockers (except lamotrigine) and some other AEDs (eg carbamazepine or phenytoin sodium) can worsen seizures in patients with CME and therefore would not be used for this indication; based on this the Subcommittee considered it inappropriate for the Special Authority criteria to require prior treatment with carbamazepine or phenytoin sodium in patients with CME. The Subcommittee considered that in practice some clinicians likely prescribe treatment for patients who have not trialed all prerequisite treatments because some of those treatments would not be clinically appropriate for individual patients.

5.18. The Subcommittee noted the evidence for perampanel for the treatment of CME as described by PTAC in its February 2021 meeting record. The Subcommittee considered that this evidence reported benefits with perampanel in this patient population and although the data were from small studies, members considered this was not unexpected for these rare conditions. The Subcommittee considered that the body of evidence for perampanel in epilepsy suggested that people with CME would receive a benefit from treatment with perampanel similar to that received by patients with PGTC, noting that about 40% of participants of Study 332 in PGTC experienced myoclonic seizures (French et al. Neurology.2015;85:950-7). However, the Subcommittee considered that patients with progressive myoclonic epilepsy would be unlikely to gain freedom from seizures with perampanel treatment.

5.19. The Subcommittee considered that the criteria proposed for PGTC would be relevant to the population with CME, reflecting appropriate prior therapies for these patients and considered that PGTC seizures should not be required in addition to myoclonic seizures in the CME group. The Subcommittee considered that most patients with CME would be targeted by the primary generalised epilepsy criteria enabling perampanel use as a later line of therapy, although Pharmac could use the following SA criteria to target patients with CME for earlier treatment with perampanel, if desired:

> **Initial application** – (complex myoclonic epilepsy). Application from any relevant practitioner. Approvals valid for 15 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has complex myoclonic epilepsy; and
> 2. Seizures are not adequately controlled by, treatment is contraindicated with, or patient has experienced unacceptable side effects from optimal treatment with at least three of the following: sodium valproate, topiramate, levetiracetam and lamotrigine.
>
> **Renewal** – (complex myoclonic epilepsy). Applications from any relevant practitioner. Approvals valid for 24 months for applications meeting the following criteria:
> 1. The patient has demonstrated a significant and sustained improvement in seizure rate or severity and/or quality of life compared with that prior to starting perampanel treatment.

General

5.20. Overall, the Subcommittee considered that the evidence for perampanel indicated that it was effective in the groups with primary generalised epilepsy and POS, although some wide confidence intervals were reported in the perampanel clinical trials which limited the accuracy of outcome estimates. The Subcommittee considered that the relative efficacy of perampanel compared with funded AEDs (eg levetiracetam and lamotrigine) was unclear due to an absence of directly comparative data. Members considered that, in general, the newer AEDs including

perampanel appear to offer about 30% improvement in seizure reduction in the refractory PGTC and POS groups.

5.21. The Subcommittee considered that the safety profile of perampanel as reported in the clinical trial evidence included adverse events that are associated with some other AEDs, such as psychiatric events including suicidal ideation, dizziness, somnolence and weight gain which can be associated with other AEDs. The Subcommittee noted that carbamazepine interacts with perampanel, significantly decreasing the concentration of perampanel and that a specific dose titration is recommended to account for this.

5.22. The Subcommittee considered that there was no clear evidence to suggest the use of therapeutic drug monitoring with perampanel. The Subcommittee considered that no additional monitoring (eg ECG or blood tests) would be required to manage a patient receiving perampanel treatment, although considered that elderly patients and those with psychiatric comorbidities would benefit from monitoring for psychiatric problems and falls. The Subcommittee considered that in current practice, patients initiated on a new AED and their GPs would be warned about the risk of ataxia and suicidality, with the GP having responsibility for identifying and differentiating any adverse drug effects from other symptoms.

5.23. The Subcommittee noted that the effective dose of perampanel was 8 mg to 12 mg with up-titration of 2 mg every two weeks. The Subcommittee considered that the mean dose of perampanel reported by the Australian PBS of 5.82 mg was possibly too low to be used as a reasonable estimate for the New Zealand population. However, the Subcommittee considered that it was unclear whether this mean dose was influenced by a small sample size, whether it was used in combination with enzyme inducing pharmaceuticals (in which case a higher dose of perampanel may be required), and in what proportions of adults and children it was used (where target dosing may differ). The Subcommittee considered that Pharmac staff could seek further information from the supplier and/or investigate the PBS data further to inform modelling of likely dose.

5.24. The Subcommittee considered that the availability of a range of AEDs with different mechanisms of action was valuable in supporting optimal treatment of people with epilepsy and considered that it appears greater benefits are achieved with combination use of AEDs that have different mechanisms of action compared with combination use of AEDs with similar action. The Subcommittee considered that perampanel would likely be used in combination with another AED(s) even if a patient experienced a reduction in seizure frequency. The Subcommittee considered that seizure freedom would be unlikely to be attained in highly refractory epilepsy and that clinicians would strive for best outcomes by continuing to trial treatments that may add some benefit. The Subcommittee considered that lacosamide usage reflected that this approach does occur in current practice. The Subcommittee noted that the magnitude of treatment benefit appears to deteriorate with subsequent treatments (Chen et al. JAMA Neurol. 2018;75:279-86). The Subcommittee considered that concomitant use in 5% of patients was a reasonable estimate to use for the New Zealand patient population who would access perampanel, if funded, noting that Chen et al. reported in their study that a fourth AED or more provided less than 5% additional probability of seizure freedom.

5.25. The Subcommittee considered that the proposed Special Authority criteria for PGE, POS and CME would together target all patients with refractory epilepsy,

including people with refractory PGE who experience seizures other than GTC and myoclonic seizures. Members considered that this was a point of difference between the Special Authority criteria recommended by PTAC (which were derived from the supplier application) and the Subcommittee, respectively. The Subcommittee considered that the Subcommittee-proposed criteria for patients with refractory PGE without GTC seizures, who were perhaps inadvertently excluded from the PTAC-recommended criteria for PGTC, could increase the number of PGE patients who might access perampanel for this indication by approximately 30% above the previous estimate for PGTC. The Subcommittee considered that it would be appropriate for the Special Authority renewal criteria for each of these three indications to be the same, as there was no apparent reason for them to differ. Members noted that Special Authority criteria may be required to manage fiscal risk, however, considered that a Special Authority would be time-consuming for clinicians and less relevant for managing fiscal risk if perampanel's cost was similar to that of funded AEDs.

5.26. The Committee considered that the table below summarises its interpretation of the most appropriate PICOs (population, intervention, comparator, outcomes) information for perampanel if it were to be funded in New Zealand for these indications. These PICOs capture key clinical aspects of the proposals and may be used to frame any future economic assessment by Pharmac staff. These PICOs are based on the Committee's assessment at this time and may differ from that requested by the applicant. These PICOs may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

	Refractory primary generalised epilepsy (includes complex myoclonic epilepsy)	**Refractory epilepsy with focal-onset seizures (FOS)**	**Refractory complex myoclonic epilepsy** (if this subgroup is for perampanel treatment earlier in the paradigm)
Population	Adult and adolescent patients from 12 years of age with refractory primary generalised epilepsy (including idiopathic generalised epilepsy, IGE, and complex myoclonic epilepsy, CME)	Patients with refractory epilepsy with partial-onset seizures	Patients with refractory complex myoclonic epilepsy
Intervention	Perampanel initiated at 2 mg daily titrated to 8 mg daily (patients can increase to 12 mg daily as tolerated)	Adjunctive perampanel initiated at 2 mg daily titrated to 4 mg to 12 mg tablets per day, once daily.	Perampanel initiated at 2 mg daily titrated to 8 mg daily (patients can increase to 12 mg daily as tolerated)
Comparator(s) (NZ context)	Currently funded AEDs (sodium valproate, levetiracetam, lamotrigine, topiramate and clobazam)	Adjunctive lacosamide tablets, twice daily.	Currently funded AEDs (valproate, levetiracetam, lamotrigine and topiramate)
Outcome(s)	Reduced seizure frequency Mortality risk reduction	Reduced seizure frequency Mortality risk reduction	Reduced seizure frequency Mortality risk reduction

Table definitions:

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

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

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

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

6. Zonisamide – epilepsy

Application

6.1. The Subcommittee considered the clinician application for zonisamide for monotherapy or adjunctive therapy for the treatment of partial epilepsy, Lennox-Gastaut Syndrome (LGS), similar epileptic encephalopathies, and severe childhood epilepsy syndromes.

- The Subcommittee noted that the applicant had:
- Expressed a preference for the open-listing of zonisamide (ie no funding restrictions)
- Proposed that zonisamide would most likely be used as a treatment option in people with partial seizure disorders alongside topiramate (ie after any three of levetiracetam, lamotrigine, carbamazepine and sodium valproate), which Pharmac staff consider represents funding in the fourth-line setting
- Further considered that if a Special Authority was required, criteria similar to lacosamide may be appropriate (which would place zonisamide at sixth-line treatment).

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

Discussion

6.3. The Subcommittee noted that PTAC reviewed the funding application for zonisamide in September 2020 and at that time, PTAC recommended that zonisamide be funded:

- with a high priority as an adjunctive treatment for refractory partial epilepsy,
- with a low priority as monotherapy for the treatment of refractory partial epilepsy, and
- with a high priority for the treatment of severe childhood epilepsy syndromes, including Lennox-Gastaut Syndrome (LGS) and similar epileptic encephalopathies.

6.4. The Subcommittee noted that in its review of the funding application, PTAC had considered that Pharmac should seek advice from the Neurological Subcommittee for the purposes of economic modelling; in particular, advice regarding:

- baseline seizure rates in the recommended patient groups in New Zealand to assess the appropriateness of a 50% reduction in seizures (noting the large variability on this in the literature),
- whether lesser seizure reductions could still provide clinically meaningful improvements for these patients with very high need, and
- the total expected number of patients who would be expected to use zonisamide and which pharmaceuticals zonisamide would be used in combination with

6.5. The Subcommittee considered that there was no recent data readily available to inform the average baseline seizure rates in individuals with refractory partial epilepsy requiring monotherapy or adjunctive therapy, or in severe childhood epilepsy syndromes including LGS and similar epileptic encephalopathies. Members considered that a large community-based epilepsy cohort study conducted in the UK may provide some data regarding seizure rates in a comparable population (Manford et al. Neurology. 1992;42:1911-7). The Subcommittee noted that clinical trials predominantly have previously used one

seizure per week as a threshold for trial eligibility and considered that this has carried forward as an informal standard for severity given even one or two seizures can significantly affect an individual (eg from the impact of this on ability to work or drive). The Subcommittee considered that patients with severe childhood epilepsy syndromes may experience several seizures per week consisting of several types (eg tonic-atonic, myoclonic, complex partial, atypical absence and generalised tonic-clonic seizures). The Subcommittee considered that in practice, it can be challenging to accurately identify the baseline seizure rate in an individual with epilepsy from which to subsequently assess treatment response.

6.6. The Subcommittee considered that a reduction in seizures would correlate to a clinically meaningful reduction in the risk of complications or death due to fewer seizures. However, the Subcommittee considered that even with a 50% reduction in seizures the occurrence of a single seizure can have serious consequences for a person with epilepsy and therefore the majority of patients would be unlikely to attain a significant change in quality of life (QoL), although a small number of patients with mild epilepsy might experience a change in QoL due to the ability to work and/or drive.

6.7. The Subcommittee considered that a 50% reduction in seizures from baseline was an outcome used in clinical trials to define a response to active treatment, as opposed to a placebo response which is reported to attain up to a 25-30% reduction in seizure frequencies in epilepsy trials. The Subcommittee therefore considered that a threshold of 30% reduction in seizures from baseline may also capture patients experiencing a placebo response and would not be appropriate to use for funding criteria renewal for zonisamide on a population level. The Subcommittee considered that in rare cases patients may attain clinically relevant reductions in seizure severity or duration, move to a less severe seizure type (eg from complex partial seizures to simple partial seizures), or experience other clinically meaningful improvements (eg in patient/carer global impression) that may align with the intent of the significant improvement according to a 50% reduction in seizures, and considered that such patients could be appropriately considered case-by-case for treatment renewal. Overall, the Subcommittee considered that it would be appropriate for funding criteria for zonisamide to require a significant and sustained benefit in order to access renewal, with a 50% reduction in seizures from baseline used as a guide.

6.8. The Subcommittee noted that zonisamide is an oral sulfonamide derivative with minimal carbonic-anhydrase effect. The Subcommittee noted that zonisamide blocks voltage-dependent sodium channels and reduces voltage-sensitive T-type calcium currents without affecting L-type calcium currents) and it has a modulatory effect on gamma-aminobutyric acid (GABA)-mediated neuronal inhibition. The Subcommittee considered that these multiple mechanisms of action may help explain the efficacy of zonisamide in epilepsy that is refractory to other antiepileptic drugs (AEDs) including other sodium channel blockers.

Partial epilepsy

6.9. The Subcommittee noted PTAC's appraisal of the evidence for zonisamide in its September 2020 record, including a Cochrane review summarising evidence of efficacy of zonisamide (vs carbamazepine and vs lamotrigine) in partial seizures (Nevitt et al. Cochrane Database Syst Rev. 2017;12:CD011412) and considered the evidence supported the use of zonisamide in partial epilepsy.

6.10. The Subcommittee considered that fourth-line use of zonisamide for partial epilepsy would be expected to reduce seizure frequency and/or severity for a proportion of patients with refractory epilepsy due to its different mechanisms of action to those of funded AEDs. The Subcommittee considered that funding a treatment with a different mechanism of action would be particularly useful for patients who are not receiving sufficient benefit on current funded treatments; noting the refractory disease state of patients who have trialled and received insufficient benefit from several AEDs differs from that of less pre-treated patients.

6.11. The Subcommittee considered that approximately 4,500 patients might access zonisamide as a fourth-line treatment, based on an epilepsy prevalence of 1% in New Zealand, two-thirds of whom would likely have partial onset seizures. Of that proportion, about 30% would be refractory and a further 50% of those would have received insufficient benefit from at least three other funded AEDs. The Subcommittee considered that about 10-20% of those trialling zonisamide (about 540 patients) might use it long-term based on 1.17% of patients gaining seizure freedom from a fourth-line AED after one year, as reported in the real-world study by Chen et al. (Chen et al. JAMA Neurol. 2018;75:279-86). The Subcommittee considered that about half of the 540 patients who might receive zonisamide long-term would otherwise have been prescribed lacosamide. The Subcommittee considered therefore that about 4,000 people with partial epilepsy would trial zonisamide for approximately six months but would be expected to subsequently discontinue zonisamide due to insufficient benefit. The Subcommittee considered that uptake of fourth-line zonisamide would be gradual and that patients would have used levetiracetam, lamotrigine and one other AED (eg carbamazepine or sodium valproate) prior.

6.12. The Subcommittee considered that, if zonisamide were funded for all patients with partial epilepsy, it would most likely be used in place of topiramate within the treatment paradigm. However, the Subcommittee considered that zonisamide could be used as an adjunctive treatment for partial epilepsy in combination with the following AEDs: topiramate in about 10% of cases requiring adjunctive treatment; carbamazepine in about 15%; and lamotrigine and levetiracetam in about 30%, respectively.

6.13. The Subcommittee considered that, if zonisamide were funded as a sixth-line treatment for partial epilepsy alongside lacosamide in the treatment paradigm, preferential use of lacosamide would likely continue due to clinician familiarity (noting its comparable efficacy and toxicity to that of zonisamide). Members considered that lacosamide and zonisamide demonstrated similar benefit and safety for partial epilespy. However, the Subcommittee considered that zonisamide's different mechanism of action to lacosamide (and other funded AEDs) would be of benefit for some patients and was an important point of difference. The Subcommittee considered that, if an adequate response was not achieved or intolerable side effects resulted from sixth-line lacosamide, zonisamide would likely be trialled (and vice versa, if initiated in the opposite sequence).

6.14. The Subcommittee considered that funding zonisamide in the fourth-line setting would be more clinically appropriate than in the sixth-line setting which would require prior treatment with more funded AEDs. The Subcommittee therefore considered that the following Special Authority criteria could target funding to patients with refractory partial epilepsy:

> **Zonisamide (partial onset epilepsy). Initial application** from any relevant practitioner. Approvals valid for 15 months for applications meeting the following criteria.

Both:

1 Patient has partial-onset epilepsy; and

2 Seizures are not adequately controlled by, or patient has experienced unacceptable side effects from, optimal treatment with at least three of the following: levetiracetam, lamotrigine, carbamazepine and sodium valproate (see Note)

Note: "Optimal treatment" is defined as treatment which is indicated and clinically appropriate for the patient, given in adequate doses for the patient's age, weight and other features affecting the pharmacokinetics of the drug with good evidence of compliance. Individuals of childbearing potential are not required to have a trial of sodium valproate.

Renewal application from any relevant practitioner. Approvals valid for 24 months where the patient has demonstrated a significant and sustained improvement in seizure rate or severity and/or quality of life compared with that prior to starting zonisamide treatment (see Note).

Note: As a guideline, clinical trials have referred to a notional 50% reduction in seizure frequency as an indicator of success with anticonvulsant therapy and have assessed quality of life from the patient's perspective.

Severe childhood epilepsy syndromes

6.15. The Subcommittee noted that the management of LGS generally follows a sequence of pharmacological treatments according to expert clinical opinion, with initial therapy using sodium valproate followed by adjunctive lamotrigine, with other subsequent adjuvant treatments; then topiramate or clobazam .

6.16. The Subcommittee considered that about half of the eligible population with severe childhood epilepsy syndromes might access zonisamide if it were funded, equating to approximately 250-280 children. Members noted this figure was based on the incidence of LGS in New Zealand (0.26 per 1,000 children at age 10) and opinion that LGS accounts for approximately 50% of childhood epileptic encephalopathies/severe epilepsy syndromes in New Zealand. The Subcommittee considered it a reasonable estimate given half of patients or clinicians may not seek to trial zonisamide in this setting as a proportion of these patients are not under intensive specialist review. Members considered that the zonisamide discontinuation rate would be similar for LGS group, as the drop-off rates for patients appeared similar in the zonisamide and placebo groups.

6.17. The Subcommittee considered that, if zonisamide were funded for LGS, it might be used ahead of levetiracetam in the treatment paradigm. However, the Subcommittee considered that zonisamide could be used as an adjunctive treatment for LGS in combination with the following AEDs: sodium valproate in about 20% of cases requiring adjunctive treatment; lamotrigine in about 20%; topiramate in about 20%; and rufinamide (although not currently funded), levetiracetam and clobazam each in about 10%. The Subcommittee noted that some patients who receive a partial response may continue to receive treatment with more than two AEDs. The Subcommittee considered that lamotrigine and sodium valproate (and rufinamide, if it were to be funded on the Pharmaceutical Schedule) would be the most common co-prescribed medicines if zonisamide were funded for LGS, due to the good body of evidence for benefits of lamotrigine, sodium valproate and rufinamide in LGS management.

6.18. The Subcommittee considered that the following Special Authority criteria could be used to target funding for zonisamide to the population with severe childhood epilepsy syndromes:

Zonisamide (severe childhood epilepsy). Initial application from any relevant practitioner. Approvals valid for 15 months for applications meeting the following criteria.

Both:

1. Patient has a severe childhood epilepsy syndrome (eg. Lennox-Gastaut Syndrome)
2. Seizures are not adequately controlled by, or patient has experienced unacceptable side effects from, optimal treatment with all of the following: lamotrigine, levetiracetam, sodium valproate, topiramate and clobazam (see Note)

Note: "Optimal treatment" is defined as treatment which is indicated and clinically appropriate for the patient, given in adequate doses for the patient's age, weight and other features affecting the pharmacokinetics of the drug with good evidence of compliance. Individuals of childbearing potential are not required to have a trial of sodium valproate.

Renewal application from any relevant practitioner. Approvals valid for 24 months where the patient has demonstrated a significant and sustained improvement in seizure rate or severity and/or quality of life compared with that prior to starting zonisamide treatment (see Note).

Note: As a guideline, clinical trials have referred to a notional 50% reduction in seizure frequency as an indicator of success with anticonvulsant therapy and have assessed quality of life from the patient's perspective.

General

6.19. The Subcommittee considered that, if zonisamide were open listed, it would likely be accessed to treat all types of refractory epilepsies (including primary generalised epilepsies, severe childhood epilepsies and juvenile myoclonic epilepsy) although uptake would be influenced by clinician preference and familiarity on whether or not to trial zonisamide.

6.20. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information zonisamide if it were to be funded in New Zealand for partial epilpesy and severe childhood epilepsy syndromes. 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	1 Patients with partial epilepsy whose seizures are not adequately controlled or have experienced unacceptable side effects from prior treatments and are seeking fourth line treatment. 2 Patients with a severe childhood epilepsy syndrome (eg. LGS) whose seizures are not adequately controlled or have experienced unacceptable side effects from prior treatments and are seeking sixth line treatment
Intervention	Zonisamide. Initial zonisamide dose 100 mg a day, followed by fortnightly increases in dosage to a target maintenance dose of 300-600 mg per day. To be taken indefinitely if tolerated and efficacious.
Comparator(s)	1 Other fourth line treatments: phenytoin and adjunctive use of topiramate, carbamazepine, lamotrigine or levetiracetam for those patients who require adjunctive treatment 2 Levetiracetam and adjunctive use of sodium valproate, lamotrigine, topiramate, levetiracetam and clobazam for those patients who require adjunctive treatment
Outcome(s)	Reduced frequency of seizures, leading to reduction in morbidity and mortality.
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.	

7. Ocrelizumab for primary progressive multiple sclerosis (PPMS)

Application

7.1. The Subcommittee considered the application from Roche Products (New Zealand) Ltd for ocrelizumab for the treatment of primary progressive multiple sclerosis (PPMS). The Subcommittee noted that the application was originally submitted in August 2017 and a resubmission was received in August 2020.

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

Discussion

Background

7.3. The Subcommittee noted that in February 2018, PTAC reviewed the funding application for ocrelizumab for the treatment of PPMS and recommended it be declined. At that time, PTAC considered that despite the high unmet health need in patients with PPMS there were significant concerns with the application, including a lack of data to establish both the safety and efficacy in this currently untreated group, and the pivotal study was perceived to have bias.

7.4. The Subcommittee noted that in June 2018, the Multiple Sclerosis Treatments Advisory Committee (MSTAC) had recommended ocrelizumab be funded with a medium priority for people with PPMS with active inflammatory disease. At that time, MSTAC considered that the statistical analysis was appropriate and that it supported treatment for PPMS, particularly in those with gadolinium enhancing lesions.

7.5. The Subcommittee noted that in November 2018, PTAC noted MSTAC's view. At that time, PTAC considered that there is a high unmet health need in patients with PPMS; however, it would need to see more robust evidence of improved health outcomes to change its previous recommendation that the application be declined.

7.6. The Subcommittee noted that PTAC reviewed the August 2020 resubmission in November 2020 and that PTAC subsequently recommended ocrelizumab be funded for PPMS with a low priority based on the high health need of people with PPMS, lack of funded treatment options, and modest evidence of benefit of ocrelizumab for this indication. At that time, PTAC considered that Pharmac could seek further advice from the Neurological Subcommittee on the clinically appropriate EDSS (Expanded Disability Status Scale) scores for Special Authority treatment initial and renewal criteria, appropriateness of the 2010 McDonald criteria as part of the entry criteria, and role of MRI in diagnosis and management of PPMS.

Access criteria

7.7. The Subcommittee **recommended** that ocrelizumab be funded with the following Special Authority criteria:

> **Initial application** — (Primary progressive multiple sclerosis) only from a neurologist or on the recommendation of a neurologist. Approvals valid for 12 months for applications meeting the following criteria:
>
> 1 Diagnosis of primary progressive multiple sclerosis, confirmed by a neurologist; and
> 2 Diagnosis must include MRI confirmation; and
> 3 Diagnosis of primary progressive multiple sclerosis by the 2017 McDonald criteria; and
> 4 Patient has an EDSS 2.0 (score ≥2 on pyramidal functions) to EDSS 6.5; and
> 5 Patient has no history of relapsing remitting multiple sclerosis
>
> **Renewal application** – (Primary progressive multiple sclerosis) only from a neurologist or on the recommendation of a neurologist. Approvals valid for 12 months for applications meeting the following criteria:
>
> 1 Patient has had an EDSS score of 2.0 to 6.5 (inclusive) at any time in the last six months (i.e. patient has walked 20 metres with bilateral assistance/aids, without rest in the last six months)

7.8. The Subcommittee noted the long-term evidence (6.5 year follow up) from the ORATORIO trial to inform a 25% reduction in EDSS progression in patients treated with ocrelizumab up to at least an EDSS of 7.0 (as noted in the November 2020 PTAC record). The Subcommittee noted in the ORATORIO trial that patients with EDSS scores of 3.0 to 6.5 were initiated on ocrelizumab. As such, the Subcommittee considered that an appropriate initial EDSS score to be eligible for funded ocrelizumab for PPMS should be between 2 and 6.5, and that this would target treatment to individuals who would benefit most from ocrelizumab.

7.9. The Subcommittee considered that it was appropriate to require a person with PPMS to have experienced one or more years of disability progression prior to receiving funded treatment (as per the 2010 and 2017 McDonald criteria). Members considered that the requirement of EDSS 2.0 for treatment initiation would not disadvantage patients as very few people are diagnosed with PPMS at a lower EDSS state with disease duration under one year.

7.10. The Subcommittee considered that the 2017 McDonald criteria (as opposed to the 2010 McDonald criteria) would be the appropriate tool to guide diagnosis. Members noted that this version is used in current practice and the key change for PPMS diagnosis in the 2017 criteria (the removal of the distinction between

symptomatic and asymptomatic MRI lesions and the use of cortical lesions) was not a substantial difference.

7.11. The Subcommittee noted that there is limited direct evidence of the use of ocrelizumab in PPMS patients with EDSS above 7.0, which in part is due to the small number of patients in this group in the ORATORIO trial. Members considered it is unlikely there will be further studies performed at higher EDSS levels. The Subcommittee noted that the supplier's resubmission requested that treatment be ceased once an EDSS of 8.5 was reached.

7.12. The Subcommittee considered the outcomes observed in lower EDSS states may apply to patients at higher EDSS level noting potential biological plausibility, however that this was conjecture. Members noted that individuals with PPMS and higher EDSS states ie. >7.5) are more likely to be elderly, Members considered that this would likely impact the ability for treatment to occur in day-case units and may result in longer admission for infusions. The Subcommittee also noted that the risk-benefit of potential adverse events (eg. severe infection) from ocrelizumab compared to the benefit that would be had at higher EDSS states would need to be carefully balanced for older individuals and/or those with high EDSS scores. However, Members also noted that even small benefits from treatment, particularly related to upper limb function were highly valuable and clinically meaningful for individuals with high EDSS scores due to the loss of lower limb mobility.

7.13. The Subcommittee considered that an appropriate renewal EDSS score would be 6.5, ie. that a patient would not be eligible to continue on funded treatment once an EDSS of 7.0 or greater was reached. The Subcommittee noted that this was in line with the main clinical trial entrance criteria (EDSS up to 6.5). The Subcommittee considered that consideration of a higher EDSS renewal (eg. 8.5 as requested by the supplier), would be inappropriate with the current lack of evidence to inform benefit. Members noted that a requirement of 'no progression' should not be required for continued treatment with ocrelizumab due to the inherently progressive nature of PPMS, even with treatment.

7.14. Members considered that any discrepancy between renewal EDSS in relapsing remitting MS (RRMS) and PPMS criteria may be contentious, particularly if not supported with relevant evidence. The Subcommittee acknowledged that the renewal criteria for MS treatments are in place to manage the high cost of treatment; although Members noted that treating MS indefinitely was not necessarily best practice.

MRI

7.15. The Subcommittee considered that MRIs are currently used in the diagnosis of PPMS but are not used regularly throughout the treatment process (unlike RRMS). The Subcommittee considered there are currently no issues with access to MRI for PPMS diagnosis, however some patients may experience delays in MRI. Members noted that if ocrelizumab were funded for PPMS that patients would be monitored for tolerability, safety and clinical effect by consultation rather than by MRI.

7.16. The Subcommittee noted that, if ocrelizumab were funded for PPMS, the supplier estimated that access to MRI scanning would limit eligibility by 50%. The Subcommittee considered that this would not be the case, however that if the Special Authority criteria required patients to have gadolinium-enhancing lesions

at baseline to access funded treatment, that this would reduce the eligible population. However, the Subcommittee noted that gadolinium-enhancing lesions were not included in the 2017 McDonald criteria and considered as such that it should not be an eligibility requirement for access to funded ocrelizumab.

General

7.17. The Subcommittee considered that the disease management costs (excluding pharmaceuticals) for each EDSS health state associated with PPMS were broadly similar to that of patients with RRMS. The Subcommittee also noted there may be different patterns of disability at lower EDSS due to relapses with incomplete recovery in RRMS.

7.18. The Subcommittee noted that the supplier provided two estimates for the elevated mortality of PPMS patients compared with the expected age-normative probability of death in NZ, based on results reported in a Canadian observational study (Kingwell et al. J Neurol Neurosurg Psychiatry. 2012;83:61-6). The Subcommittee considered that the revised mortality estimate provided by the supplier in 2020, compared with 2018, provided cost effectiveness results that were heavily impacted by patients pooling and spending considerable time in an EDSS 9 health state and incurring significant health sector costs. The Subcommittee considered the mortality estimate provided by the supplier in 2020 is likely to be inaccurate beyond two years. The Subcommittee considered the median time spend in EDSS bands in the Welsh data was more reasonable (Harding et al. Mult Scler Relat Disord. 2018;25:186-191). Overall, the Subcommittee considered the 2018 mortality rates and time spent in each EDSS health state to be more plausible.

7.19. The Subcommittee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for ocrelizumab if it were to be funded in New Zealand for PPMS. 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 Subcommittee'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	Patient with diagnosed PPMS (eligibility as per proposed special authority criteria).
Intervention	Ocrelizumab 600 mg IV every six months.
Comparator(s) (NZ context)	Best supportive care (no current funded pharmaceutical treatments).
Outcome(s)	Reduction in rate of disease progression (measured by EDSS). Quality of life improvements Health sector savings from delayed progression
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: 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). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	