

# Record of the joint Neurological and Mental Health Subcommittee Meeting held on 7 February 2019

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## In attendance

### *Present from the Subcommittee:*

Mark Weatherall (Chair, PTAC Chair)  
David Chinn  
John Fink  
Sean Hanna (PTAC member)  
Richard Hornabrook  
Ian Hosford (PTAC member)  
David Menkes  
John Mottershead  
Giles Newton-Howes (PTAC member)  
Ian Rosemergy  
Paul Timmings

### *Apologies:*

Verity Humberstone  
Jeremy McMinn  
Cathy Stephenson

### *Present from PHARMAC:*

Adrienne Martin  
Sarita Von Afehl  
John Wyeth  
Peter Murray  
Dee Alexander  
Geraldine MacGibbon  
Hannah Hoang  
Bronwyn Locke (part of meeting)  
Scott Garret (part of meeting)  
Hayden Spencer (part of meeting)

## Summary of outcome

2.3 The Subcommittee, having considered the consultation feedback and other material presented to it, was supportive of the proposal to move to one funded brand of lamotrigine (Logem), with implementation support as discussed below.

# 1. Lamotrigine

## Background

- 1.1 The Mental Health and Neurological Subcommittees (hereafter collectively referred to as the Subcommittee) jointly considered a paper from PHARMAC staff seeking further advice regarding a proposal to move to one funded brand of lamotrigine (Logem) in light of concerns raised during a consultation process run by PHARMAC in August 2018 regarding the proposed change.

## Outcome

- 1.2 The Subcommittee, having considered the consultation feedback and other material presented to it, was supportive of the proposal to move to one funded brand of lamotrigine (Logem), with implementation support as discussed below.

## Discussion

### *Literature*

- 1.3 The Subcommittee considered the publications previously reviewed by the Neurological Subcommittee of PTAC in [November 2015](#), the publications provided to PHARMAC during correspondence with Medsafe, the publications provided to PHARMAC during the consultation process carried out in August 2018, the publications identified via a literature review conducted by PHARMAC staff in January 2019, and additional publications identified by Members of the Subcommittee. The following publications were reviewed:

- 1.3.1 Andermann et al. *Epilepsia*. 2007;48:464-9.
- 1.3.2 Atif et al. *Springerplus*. 2016;5:182.
- 1.3.3 Bautista et al. *Epilepsy Res*. 2011;95:158-67.
- 1.3.4 Berg et al. *JAMA Neurology*. 2017;74:919-926.
- 1.3.5 Berg MJ. *Neurology*. 2007;68:1245-1246.
- 1.3.6 Boylan LS. *Neurology*. 2009;72:1876-7.
- 1.3.7 Carbon M & Correll CU. *CNS Drugs*. 2013;27:353-65.
- 1.3.8 Chaluvadi et al. *Epilepsia* 2011;52:810-5.
- 1.3.9 Contin et al. *Epilepsy Res*. 2016;122:79-83.
- 1.3.10 Crawford et al. *Seizure*. 2006;15:165-76.
- 1.3.11 Desmarais JE et al. *CNS Neurosci Ther*. 2011;17:750-760.

- 1.3.12 Erickson et al. *Epilepsia* 2011;52:1365-71.
- 1.3.13 Erickson et al. *Epilepsia*. 2011;52:1365-71.
- 1.3.14 Gagne et al. *Clin Pharmacol Ther* 2010;88:347-53.
- 1.3.15 Hansen et al. *Epilepsy Res* 2013;106:237-43.
- 1.3.16 Hartung et al. *CNS Drugs* 2012;26:707-16.
- 1.3.17 Holtkamp & Theodore. *Epilepsia*. 2018;59:1273-81.
- 1.3.18 Holtkamp M. *Nat Rev Neurol*. 2019;15:8-9.
- 1.3.19 Kesselheim et al. *Drugs* 2010;70:605-21.
- 1.3.20 Kesselheim et al. *JAMA Intern Med*. 2013;173:202-8.
- 1.3.21 Kesselheim et al. *Neurology*. 2016;87:1796-1801.
- 1.3.22 Kinikar et al. *Ann Pharmacother* 2012;46:650-8.
- 1.3.23 Kjoenniksen et al. *Pharm World Sci*. 2006;28:284-9.
- 1.3.24 Krauss GL. *JAMA Neurol*. 2017;74:900-901.
- 1.3.25 Kwan P & Palmini A. *Epilepsy Behav*. 2017;73:166-172.
- 1.3.26 Labiner et al. *Neurology*. 2010;74:1566-74.
- 1.3.27 Lalic et al. *Drugs R D*. 2011;11:53-60.
- 1.3.28 Lang et al. *Ann Neurol*. 2018; doi: 10.1002/ana.25353. [Epub ahead of print].
- 1.3.29 LeLorier et al. *Curr Med Res Opin*. 2008;24:1069-81.
- 1.3.30 Lessing et al. *Appl Health Econ Health Policy* 2014;12:537-46.
- 1.3.31 Lessing et al. *Value Health*. 2015;18:646-654.
- 1.3.32 Liow et al. *Neurology*. 2007;68:1249-50.
- 1.3.33 Makus KG & McCormick J. *Clin Ther*. 2007;29:334-41.
- 1.3.34 Miller JE et al. *Neurology*. 2007;69:1806-8.
- 1.3.35 Nielsen et al. *Epilepsy Behav*. 2008;13:127-30.
- 1.3.36 Patel et al. *Epilepsy Res*. 2012;98:269-72.

- 1.3.37 Polard et al. *Pharmacoepidemiol Drug Saf* 2015;24:1161-9.
- 1.3.38 Privitera et al. *Lancet Neurol.* 2016;15:365-72.
- 1.3.39 Privitera M. *Neurol Clin Pract.* 2013;3:161-164.
- 1.3.40 Privitera MD. *Epilepsy Curr.* 2008;8:113-7
- 1.3.41 Rahman et al. *Epilepsy Res.* 2017;135:71-78.
- 1.3.42 Rascati et al. *Pharmacotherapy.* 2009;29:769-74.
- 1.3.43 Sabroe et al. *Acta Neurol Scand.* 2008;117:428-31
- 1.3.44 Shcherbakova et al. *CNS Drugs.* 2014;28:1047-58
- 1.3.45 Srichaiya et al. *Clin Ther.* 2008;30(10):1822-51
- 1.3.46 Shin et al. *Int J Clin Pharmacol Ther* 2014;52:1017-22.
- 1.3.47 Talati et al, *Pharmacotherapy* 2012;32:314-22.
- 1.3.48 Ting et al. *Epilepsia* 2015;56:1415-24.
- 1.3.49 Vari et al. *Clin Drug Investig.* 2016;36:87-91.
- 1.3.50 Vossler et al. *Epilepsy Curr.* 2016;16:209-211.
- 1.3.51 Wick, J.Y. (2014). *Switching Antiepileptic Drugs: Benefits Versus Risks.*
- 1.3.52 Wilner AN. *Epilepsy Behav.* 2004;5:995-8.
- 1.3.53 Yamada & Welty. *Ann Pharmacother* 2011;45:1406-15.
- 1.3.54 Zachry et al. *Epilepsia.* 2009;50:493-500.
- 1.4 The Subcommittee noted that there was a significant body of published evidence regarding changing between lamotrigine brands. The Subcommittee considered that some of the smaller case series reported that brand changes of lamotrigine were associated with loss of seizure control and adverse reactions (e.g. [Makus KG & McCormick J. Clin Ther. 2007;29:334-41](#)). However, the majority of the evidence provided by studies of higher quality, and less subject to bias, such as prospective and retrospective cohort studies, and systematic reviews of the broad range of evidence, reported that there was unlikely to be important clinical risks as a result of changing between brand and generic lamotrigine for the majority of patients (e.g. [Lessing et al. Appl Health Econ Health Policy 2014;12:537-46](#); [Hartung et al. CNS Drugs 2012;26:707-16](#); [Yamada & Welty. Ann Pharmacother 2011;45:1406-15](#)).
- 1.5 The Subcommittee noted a case-control study results from the Lang et al 2018

retrospective study (Lang. *Ann Neurol.* 2018; doi: 10.1002/ana.25353. [Epub ahead of print]), that, reported an increased risk for recurrent seizures in previously seizure free patients after changing the manufacturer of the same antiepileptic drug (although not specifically for lamotrigine) in a sample of 3650 patients from Germany. The Subcommittee noted that depression and anxiety as comorbidities were adjusted for in the study to avoid a confounding effect. However, the Subcommittee noted that the study had an open-label design, and therefore considered that baseline anticipatory (pre-switch) anxiety could have led to seizures being reported more frequently.

- 1.6 The Subcommittee considered an article in response to the Lang et al publication (Holtkamp M. *Nat Rev Neurol.* 2019;15:8-9) highlighting that the pharmacology of branded and generic Antiepileptic Drugs (AED) does not differ sufficiently to explain the observations of Lang et al. raising the possibility that seizure worsening after changing may be a result of patient non-adherence to treatment.
- 1.7 The Subcommittee noted the results of three prospective clinical trials funded by the US Food and Drug Administration, which investigated the bioequivalence of brand name lamotrigine and/or generic lamotrigine products.
  - 1.7.1 The Subcommittee noted the EQUIGEN Single-Dose Study in which 50 adults with epilepsy received a single 25 mg dose of branded and generic lamotrigine over six study periods (each product assessed twice) ([Berg et al. \*JAMA Neurology.\* 2017;74:919-926](#)). The Subcommittee noted that the three drugs were considered bioequivalent due the 90% confidence intervals for  $C_{max}$  and AUC being within the equivalence limits (80% to 125%).
  - 1.7.2 The Subcommittee noted the EQUIGEN Chronic-Dose Study, in which 35 adults with epilepsy were randomly allocated to one of two treatment sequences comprising four study periods of 14 days each in order to compare the bioequivalence of two generic lamotrigine products ([Privitera et al. \*Lancet Neurol.\* 2016;15:365-72](#)). The Subcommittee noted that the 90% confidence intervals for  $C_{max}$  and AUC were within equivalence limits (80% to 125%).
  - 1.7.3 The Subcommittee noted the BioEquivalence in Epilepsy Patients (BEEP) study in which “generic-brittle” (defined in section 2.13 below) patients with epilepsy were repeatedly switched between brand name lamotrigine and generic lamotrigine ([Ting et al. \*Epilepsia\* 2015;56:1415-24](#)). The Subcommittee noted that the 90% confidence intervals for AUC,  $C_{max}$ , and  $C_{min}$  fell within the conventional equivalence limits (80% to 125%).
- 1.8 The Subcommittee considered that although the Logem brand of lamotrigine was not specifically included in the three prospective clinical trials noted above ([Berg et al. \*JAMA Neurology.\* 2017;74:919-926](#), [Privitera et al. \*Lancet Neurol.\* 2016;15:365-72](#), [Ting et al. \*Epilepsia\* 2015;56:1415-24](#)), similar results could be expected in the event of a change to Logem, given Logem has been assessed to be bioequivalent to the innovator brand as part of its registration by Medsafe.

- 1.9 The Subcommittee considered the results of three large retrospective analyses which investigated the outcomes of patients who had changed from brand name to generic AEDs.
- 1.9.1 The Subcommittee considered a retrospective analysis of public-payer pharmacy-claims database from Ontario, Canada, which investigated switchback rates and the implications of changing from branded to generic lamotrigine in 1,354 patients ([Andermann et al. Epilepsia. 2007;48:464-9](#)). The Subcommittee noted that 12.9% of patients prescribed generic lamotrigine switched back to brand-name lamotrigine, which was lower than the switchback rates for other AEDs. The Subcommittee noted that the authors reported that the switch back rates may indicate increased risk of toxicity or loss of seizure control. However, the Subcommittee considered that due to the nature of the trial design the reasons for patients switching back were not able to be determined.
- 1.9.2 The Subcommittee noted a retrospective analysis of medical and pharmacy claims data from Quebec, Canada, which investigated the proportion of patients changing back from generic to brand name lamotrigine and medical resource utilization among 671 patients treated with lamotrigine ([LeLorier et al. Curr Med Res Opin. 2008;24:1069-81](#)). The Subcommittee noted that 27.5% of patients who changed from brand-name to generic lamotrigine switched back to the branded medication. The Subcommittee also noted that generic lamotrigine use was associated with a 5.1% higher mean daily dose of lamotrigine, a higher utilization rate of medical services, and a longer hospital length of stay. The Subcommittee noted that the authors reported that while the results of the study may signal reduced clinical effectiveness or increased side effects associated with generic lamotrigine, the study (due to the nature of its design) did not have access to medical claims data to evaluate the impact on medical services.
- 1.9.3 The Subcommittee considered a retrospective analysis using national health collections and prescription records from New Zealand, which investigated switch behaviour, changes in utilisation of healthcare services, and mortality among 1,655 patients receiving lamotrigine ([Lessing et al. Appl Health Econ Health Policy 2014;12:537-46](#)). The Subcommittee noted that 361 patients (21.8%) were reported to have switched from brand name lamotrigine to a generic. The Subcommittee noted that 60% of those that switched made a single switch to generic lamotrigine with no further switches throughout the study, 30% made one further switch only (either generic to generic or generic to originator) and the remaining 10% made three or more successive switches. The Subcommittee noted that approximately one quarter of the 361 patients who switched to generic lamotrigine switched back to brand name lamotrigine, and that of these switch-backs, 3% occurred within 30 days of the first switch with a mean time to switch-back of 16 days. The Subcommittee noted that the study was not designed to assess the reasons for why patients switched back to brand name lamotrigine. However, the Subcommittee considered that no differences in healthcare resource utilisation or health outcome measures (including emergency department visits, specialist appointments, hospital

admissions, use of other antiepileptic medicines and death) were identified between patients who changed from brand to generic lamotrigine and those who did not switch.

- 1.9.4 The Subcommittee considered that the study conducted by Lessing et al (2014) was the most robust and directly relevant study to the funding change proposal.
- 1.10 The Subcommittee noted that, due to the nature of the disease (epilepsy), there is a risk of seizure recurrence among patients who have been seizure free for a prolonged period, even whilst receiving a stable treatment regimen. The Subcommittee noted data from two studies reporting seizure recurrence in 7% to 22% of patients who had been seizure-free, and on treatment, for at least two years ([Medical Research Council Antiepileptic Drug Withdrawal Study Group. Lancet. 1991;337:1175-80](#)), ([Lossius et al. Epilepsia. 2008;49:455-63](#)). Based on this evidence, Members considered that there would be seizure recurrence for a proportion of patients who are currently seizure free, and on treatment, whether or not there was a change of brands (should the proposal go ahead). The Subcommittee considered that it would be reasonable to expect the number of patients for whom this would occur in New Zealand would be similar to that reported in the two studies noted above ([Medical Research Council Antiepileptic Drug Withdrawal Study Group. Lancet. 1991;337:1175-80](#)), ([Lossius et al. Epilepsia. 2008;49:455-63](#)) whether or not there is a brand change for lamotrigine. However, Members considered that it would be likely that a small number of patients would attribute this to a brand change should such a change occur.
- 1.11 The Subcommittee noted a study in which 121 adult patients with epilepsy completed a survey regarding whether they changed from brand name to generic AEDs and whether they experienced poorer seizure control and increased side effects ([Bautista et al. Epilepsy Res. 2011;95:158-67](#)). The Subcommittee noted that 25.7% of patients who changed to generic AEDs reported increased seizure frequency, and that this was associated with high seizure count and scores on the Beliefs About Medicines General questionnaire (BMQ-G). The Subcommittee considered that requiring all patients to undertake the BMQ-G would not be practical, but that ensuring patients with high seizure counts are adequately supported through any brand change may improve outcomes for these patients.
- 1.12 The Subcommittee noted that the BEEP study (Ting et al. 2015) included patients identified as “generic brittle”, which was defined as patients who may have a potential problem with changing to a generic brand by virtue of (1) a history of reported prior exacerbations of seizures or side effects following AED formulation changes; (2) intolerable AED side effects within the last year prior to study; or (3) refractory seizures within the last year prior to study, which could reflect clinical sensitivity to slightly higher AED peak plasma concentration or slightly lower drug exposure, respectively. The Subcommittee noted that few participants had seizure exacerbations or tolerability issues with brand changing, despite being ‘generic brittle’. The Subcommittee considered that this study was conducted in a double-blind manner, which would not be the case with a real-world brand change as patients would be aware of the change and could therefore potentially be subject to a placebo effect.

- 1.13 The Subcommittee noted that while there has been significant research conducted to investigate the effect of brand changing for patients with epilepsy, that there is a little or no evidence regarding the effects of changing on patients who use lamotrigine for non-epilepsy indications, predominantly mental health conditions.
- 1.14 In summary, the Subcommittee considered that, based on the available evidence, there was no pharmacological reason to suggest there would be a clinical problem with changing brands of lamotrigine for patients with epilepsy or mental health conditions. The Subcommittee considered that patients experience adverse events (e.g. breakthrough seizures) even when there is no brand change. The Subcommittee considered that in the event of a brand change there would be patients who experience adverse events that would attribute these to the change, and that factors likely to contribute to this perception could include reduced adherence, nocebo, or other psychological factors. The Subcommittee considered that the literature supports careful management of patients with epilepsy through any brand change process for lamotrigine, ensuring adequate information, education, and reassurance is provided to healthcare professionals and the patients. The Subcommittee considered that this approach should also apply to those with mental health conditions.

#### *Lamotrigine pharmacy dispensing data*

- 1.15 The Subcommittee noted dispensing data provided by PHARMAC that indicates that 52% of patients with epilepsy receiving lamotrigine and 46% of patients receiving lamotrigine for other indications in New Zealand in 2018 have changed brands previously at the pharmacy level. The Subcommittee noted that some patients have changed brands more than ten times. The Subcommittee considered that moving to sole supply of one brand of lamotrigine would reduce future inadvertent and uncontrolled brand changing from taking place.
- 1.16 The Subcommittee noted that Logem is the least frequently dispensed brand of lamotrigine currently funded in New Zealand and that there would, therefore, be a large proportion of patients required to undergo a brand change if the proposal to fund the Logem brand only goes ahead.
- 1.17 The Subcommittee noted that a small number of patients (n=~1000) were dispensed both lamotrigine and venlafaxine in 2018 and considered that if a patient experienced considerable anxiety and emotional distress with the recent venlafaxine brand change then they may also have difficulties with anxiety and emotional distress during any lamotrigine brand change.

#### *The United Kingdom (UK) Medicines and Healthcare products Regulatory Authority (MHRA)*

- 1.18 The Subcommittee noted that the Medicines and Healthcare products Regulatory Authority (MHRA) advice regarding categorisation of antiepileptic drugs when considering brand changing was updated in 2017. The Subcommittee noted that the MHRA included lamotrigine in Category 2 (drugs that do not fit into category one or three) of its guidance on prescribing AEDs. ([MHRA. Drug Safety Update volume 11, issue 4; November 2017:5](#)). The Subcommittee considered that this

was an appropriate category and that with regards to the NZ health system context, any brand change for lamotrigine needs to be accompanied by the appropriate level of support and reassurance for patients and health care professionals. The Subcommittee noted that the MHRA advice, regarding categorisation of antiepileptic drugs when considering brand changing, had been updated in 2017.

- 1.19 With regards to all other AEDs, the Subcommittee considered that the updated MHRA advice did not change the views previously expressed at the November 2015 Neurological Subcommittee meeting.

#### *Consultation feedback*

- 1.20 The Subcommittee considered the feedback submitted during the August 2018 consultation process, noting that the majority of Health Care Professionals were generally supportive of the proposal and that concerns regarding the potential and consequences for loss of seizure control or mood destabilisation were raised by Medsafe, consumers, consumer groups and pharmaceutical suppliers.
- 1.21 The Subcommittee noted that New Zealand Transport Agency, in its consultation feedback, considered that a change in brand of lamotrigine did not constitute a change in treatment and that risk from changing brands would be extremely low.
- 1.22 The Subcommittee noted that a number of consultation responses were from carers of children/adolescents with epilepsy and considered that it is important to be aware of the impact that brand changes can have not only on the person taking the medicine but also on the family/whanau.
- 1.23 The Subcommittee noted that the majority of the references provided by Medsafe had already been considered at its November 2015 meeting, but thanked Medsafe for the opportunity to review the identified literature. The Subcommittee noted the concerns highlighted by Medsafe regarding the potential and consequence for loss of seizure control as a result of a brand change for lamotrigine and considered that the Subcommittee had formed its view (of support for the proposal to change brands), based on its own assessment of the literature.

#### *Lamotrigine level monitoring*

- 1.24 The Subcommittee noted that there is some suggestion in the literature that AED levels could be monitored before and after a brand change to ensure there are no significant fluctuations in plasma lamotrigine levels due to adherence ([Holtkamp & Theodore. \*Epilepsia\*. 2018;59:1273-1281](#)). The Subcommittee considered that routine implementation of lamotrigine levels during any brand change would be unnecessary as the majority of patients would be likely to remain adherent to treatment throughout the change.
- 1.25 The Subcommittee further noted a retrospective analysis that investigated the intrasubject variation in plasma concentrations of lamotrigine, which reported that there is significant inter-day variability in lamotrigine plasma concentrations even in patients stabilized on brand name lamotrigine ([Contin et al. \*Epilepsy Res\*. 2016;122:79-83](#)). The Subcommittee considered that testing plasma levels of

lamotrigine would, therefore, be unlikely to be indicative of whether a patient is not tolerating a brand change.

- 1.26 The Subcommittee considered that monitoring of lamotrigine levels should, in the majority of cases, only be done by specialists and that, in general, it is used as a check for adherence, possible toxicity, and for monitoring purposes in some pregnant people. The Subcommittee noted that it is not a routine test that is performed to help with achieving clinical outcome and has limited clinical utility.

### *Implementation activities to support a brand change*

- 1.27 The Subcommittee noted feedback provided by Medsafe regarding vulnerable patients. The Subcommittee noted that Medsafe had suggested that general practitioners (GPs) should refer the most vulnerable patients for specialist oversight of a brand change; and that Medsafe considered that, for patients with epilepsy, the most vulnerable were those that were seizure-free and those with labile seizures. The Subcommittee considered that this was too broad a definition of vulnerable patients, and that referral of all such patients to a specialist would place an unnecessary and significant burden on specialist providers. The Subcommittee considered that generally, the majority of patients with unstable epilepsy are known to Neurology services. The Subcommittee considered that clinical judgement regarding vulnerable patients, should there be a brand change, should continue to be used by GPs, who could either contact or refer a patient with epilepsy or a mental health condition to specialist services if they considered it to be clinically necessary.
- 1.28 The Subcommittee considered that patients receiving lamotrigine for reasons other than epilepsy were likely prescribed it for mental health disorders such as bipolar affective disorder, mood stabilisation, behavioural disorders and schizoaffective disorder. Members considered that a small number of patients could also be taking lamotrigine for trigeminal neuralgia. With regards to a brand change of lamotrigine in patients with mental health conditions or trigeminal neuralgia, the Subcommittee considered that there was no physiological reason that these patients should be considered differently to patients taking it for epilepsy.
- 1.29 Although unlikely, the Subcommittee considered that the clinical symptoms that could result, should someone with epilepsy experience a reduction in bioavailability of lamotrigine, include: aura, seizures, or myoclonic jerks. For people taking lamotrigine for a mental health condition, the Subcommittee considered these symptoms would likely be similar to a person's early warning signs of mood instability and could present in idiosyncratic ways (depending on the individual). Conversely, the Subcommittee considered that the clinical symptoms that could result, should someone with epilepsy or a mental health disorder experience an increase in bioavailability of lamotrigine, could be headache, nausea, tremor, dizziness, irritability, blurred vision or visual disturbances. The Subcommittee considered that these were also the symptoms that could be experienced should a patient need an adjustment of dose or consideration of a treatment change. The Subcommittee considered that Health Care Professionals should be reminded of this and that patients should be informed of when to contact their health care professionals and/or mental health support services.
- 1.30 The Subcommittee considered that consequences of a seizure, for a patient with a driver licence, could be loss of their drivers licence for a period of 12 months. Members considered that it is possible, depending on the circumstances, to have the period of suspension from driving reduced from 12 months to six months. Members considered that this occurs via application from the treating Neurologist to NZTA on a case by case basis, citing reasons why a shorter stand down period might be valid (e.g. evidence of decreased lamotrigine levels) and explains the action taken, e.g. correction by dose adjustment. The Subcommittee considered

that while it's possible that in this circumstance a patient may attribute the seizure to a brand change (should the proposal go ahead), breakthrough seizures can happen even when a patient hasn't changed brands and it would be very difficult to determine the cause. The Subcommittee considered that it would be very unlikely for someone with epilepsy to be a professional driver as this requires a seizure free period of five years, while taking no antiepileptic treatment.

1.31 The Subcommittee considered that people with epilepsy and mental health conditions are involved in a range of employment situations and that it was difficult to determine if there were any specific implementation activities supporting a brand change that could be targeted to these situations.

1.32 The Subcommittee considered the potential implementation activities planned by PHARMAC staff, should the proposal go ahead, were wide ranging and noted that they included (but were not limited to) the following activities:

- Written PHARMAC resources specifically for prescribers, pharmacists and patients to support a change in brand.
- Consideration to covering primary care appointment fees for those patients requiring specific support with their lamotrigine brand change.
- PHARMAC website information, including a video providing lamotrigine brand change information.
- Supporting consumer-facing organisations who work with people in the community changing their brand of lamotrigine.
- Regular meetings with CARM, Medsafe and PHARMAC to ensure consistency of health sector approach.
- Development of a written resource for primary healthcare professionals, outlining how to support patients with a change and any impacts.
- Consideration of an alternative PHARMAC funding mechanism for patients to remain on a particular brand of lamotrigine if unable to be transitioned to a new brand.

1.33 The Subcommittee considered that the implementation activities (noted above) that PHARMAC staff were planning, should a brand change be approved, seemed appropriate. Members considered that there was a risk of causing unnecessary anxiety about the change if too much emphasis was placed on the change and that caution should be taken with the amount of information provided to patients upfront. Members noted that some patients would welcome more information and it should be provided to them if desired.

1.34 The Subcommittee considered that a three to six month transition period for the brand change was reasonable (should the proposal go ahead). Members highlighted that if a patient with epilepsy or a mental health condition is relatively stable then they may only see their GP once a year and, therefore, patients would ideally be informed about a change in brand when they phone up for a repeat prescription; however, this is not always practical. The Subcommittee considered that for this reason it is important to ensure that appropriate counselling occurs at a pharmacy level and prescribers are provided with appropriate consumer-focused information to discuss a brand change with their patients.

- 1.35 The Subcommittee considered that, in addition to monitoring CARM reports and hospital admissions, conducting a prospective cohort study could help monitor for breakthrough disease during any brand change, but noted that this would be highly costly and time consuming and likely impractical to implement.
- 1.36 Members considered that adherence is the most modifiable risk factor related to seizure recurrence and mental health relapse, and that any implementation activity in the event of a brand change needed to support good adherence practices.

*Exceptional circumstances*

- 1.37 The Subcommittee noted PHARMACs Exceptional Circumstances Framework and that the Framework includes the Named Patient Pharmaceutical Assessment (NPPA) Policy and other processes through which PHARMAC considers exceptional circumstances.
- 1.38 The Subcommittee considered that there is likely to be a subset of epilepsy and mental health patients for whom a brand change could be difficult, but that identifying these patients prior to any change would be challenging.
- 1.39 The Subcommittee considered that pregnant patients, and some children, with epilepsy may have difficulty with a brand change depending on their individual circumstances, but that these patients should already be under the care of a specialist who could help them through any brand transition. In addition, the Subcommittee considered that there may be a small number of patients with epilepsy and mental health conditions, also under specialist care, who have previously experienced clinical effects when changing brands due to small differences in bioavailability. The Subcommittee considered that the majority of these patients would be able to be managed via an adjustment in dose (should the proposal go ahead).
- 1.40 Subcommittee noted the 2017/18 venlafaxine brand change, and that requests for specific brands for patients who had difficulties with the change had been managed via the NPPA pathway. The Subcommittee noted that so far 49 NPPA applications had been received for venlafaxine, of which two had been approved and three applications were pending at the time of the meeting. Members noted that a large amount of the applications received did not include sufficient relevant information to be adequately assessed.
- 1.41 The Subcommittee considered that a mechanism was needed for PHARMAC to consider patients with epilepsy or other conditions for whom any lamotrigine brand change may not be appropriate or has not been tolerated. The Subcommittee considered that, based on the venlafaxine numbers and the literature reviewed, the numbers of patients for whom this would apply to would likely be low (less than 100).
- 1.42 The Subcommittee considered that the NPPA pathway could be used in the event of a brand change to consider patients who have been unable to successfully change lamotrigine brands but that a specific form for lamotrigine, as opposed to the NPPA form, may be useful to assist applying clinicians with providing the

relevant information.

- 1.43 The Subcommittee considered that, in the event of a brand change, if the numbers of applications were higher than expected and/or the rationale for requests became difficult to assess via the NPPA pathway, then a Panel of experts could be put in place to assess applications.

*Overall Summary*

- 1.44 The Subcommittee considered all of the consultation feedback, including the concerns raised by Medsafe with regards to the possibility of an increase in breakthrough seizures attributable to a brand change, and considered that based on a full review of the available evidence, there was no pharmacological reason to suggest there would be a clinical problem with changing brands of lamotrigine for patients with epilepsy or mental health conditions.
- 1.45 The Subcommittee considered that there would be patients who experience adverse events, e.g. breakthrough seizures, even when there is no brand change. The Subcommittee considered that in the event of a brand change there would be patients who experience adverse events that would attribute these to a brand change, and that factors likely to contribute to this perception could include reduced adherence, nocebo, or other psychological factors
- 1.46 The Subcommittee considered that ensuring adequate information, education, and reassurance to healthcare professionals and patients would be required to support patients with epilepsy or a mental health condition should there be a brand change for lamotrigine.
- 1.47 The Subcommittee considered that it was supportive of the proposal to move to one funded brand of lamotrigine (Logem), with implementation support as discussed above

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Mark Weatherall, Chair

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Date