Independent Review of PHARMAC's Lamotrigine Sole Supply Decision

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1.0 INTRODUCTION

1.1 The Pharmaceutical Management Agency (PHARMAC) is the crown entity responsible for deciding which medicines and medical devices are publicly funded in New Zealand. PHARMAC's objectives include securing the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of available funding.[1]

1.2 On 29 March 2019, PHARMAC made a decision to award the sole supply of the drug lamotrigine to a single brand, Logem, supplied by Mylan (the **"Sole Supply Decision**").[2]

1.3 Lamotrigine is an anticonvulsant medicine used for the treatment of epilepsy and some mental health conditions. Lamotrigine is currently used by approximately 12,500 people in New Zealand. Prior to the Sole Supply Decision, three brands of lamotrigine were funded, one of which was Logem. The Sole Supply Decision meant that approximately 11,000 people would need to change the brand of lamotrigine they had been using in order to continue to receive funded lamotrigine.

1.4 Following the Sole Supply Decision, PHARMAC implemented a five month transition period where the three brands of lamotrigine continued to be funded while measures were taken to support the implementation of the Sole Supply Decision. On 1 October 2019, Logem became the only funded brand of lamotrigine in New Zealand.

1.5 Throughout October and November 2019 there was increasing media and public interest in the move to the one brand of lamotrigine. The Centre for Adverse Reactions Monitoring (**CARM**) were reporting notifications of adverse reactions relating to the switch by patients to Logem. On 12 November 2019, Medsafe issued a monitoring communication concerning suspected adverse reaction reports in relation to lamotrigine which included three deaths. Those deaths, and subsequently further deaths, have been referred to the Coroner.

1.6 On 15 November 2019 PHARMAC announced that it was widening its 'exceptional circumstances' criteria to make it easier for patients to remain on their established brand of lamotrigine.

1.7 In February 2020, I was appointed by PHARMAC to conduct an independent review of the Sole Supply Decision. The terms of reference for the review are attached as **Appendix 1**. The purpose of the review has been to provide an independent view on whether PHARMAC's decision making and implementation processes in relation to the Sole Supply Decision were appropriate. I have been asked to provide findings in relation to three key questions:

a. Was the decision making process, including preliminary steps, followed by PHARMAC in relation to the lamotrigine Sole Supply Decision appropriate?

b. Was the design and execution of PHARMAC's implementation process for the lamotrigine Sole Supply Decision appropriate?

[1] New Zealand Public Health and Disability Act 2000, s 47(a).
[2] The Sole Supply Decision related to the 25mg, 50mg, and 100mg dispersible tablets. The 2mg and 5mg dispersible tablets (mainly for paediatric use) were unaffected by the Sole Supply Decision.

c. Given PHARMAC's role in the health sector, are there areas in which PHARMAC could improve its decision making and implementation processes for future brand changes, and if so, what are these?

1.8 The review is not intended to be a reassessment of the substantive aspects of the Sole Supply Decision – but I was asked to include matters such as the sufficiency of the information provided to the decision maker.

1.9 Any possibility that the Sole Supply Decision has caused, or contributed to, the death of any person is a matter for the Coroner. I have neither investigated, nor formed any views on, the possibility of any such connection.

1.10 Prior to commencing the review, I advised PHARMAC that I felt that I would be assisted by engaging a clinical advisor to provide me with independent clinical guidance and advice. Associate Professor Matthew Doogue, a clinical pharmacologist and endocrinologist was engaged as clinical advisor. I have received advice from A/Prof Doogue and I refer to this advice throughout this report. A/Prof Doogue's advice is attached in full, as **Appendix 2.**

1.11 To enable me to conduct the review, PHARMAC has given me full access to all documentation relating to the making, and implementation, of the Sole Supply Decision. During the course of the review, I have identified additional information that I have felt would benefit the review. All information that I have requested from PHARMAC has been provided.

1.12 As part of the review, I have met and interviewed a number of PHARMAC representatives. A full list is set out in **Appendix 3**. There have been no restrictions put on me in seeking to discuss this matter with any PHARMAC representative, and all who I have spoken to have engaged with me openly and constructively.

1.13 At the commencement of the review, I raised the possibility with PHARMAC that, during the course of the review, it might become apparent that discussions with interested persons outside PHARMAC may assist me. PHARMAC was willing to facilitate that, if I felt it necessary. As matters have transpired, and subject to the comments in the following paragraph, I have not felt that it is necessary to speak to any other interested persons in order to respond to the matters I have been asked to review. However, throughout the review I have been acutely aware that the issues I have considered relate to health consumers who have been directly impacted by the Sole Supply Decision. The views of some of these consumers, their families, and their representatives, have been clearly and coherently set out in the material that I have reviewed, and I have considered these views carefully.

1.14 I submitted a draft report to PHARMAC on 24 April 2020. Soon after submitting the draft report, I was informed by PHARMAC that a paediatric neurologist had contacted PHARMAC and had requested that they contact the independent reviewer to discuss the lamotrigine brand change decision. I subsequently had two telephone conversations with the paediatric neurologist and received written correspondence. In reaching my final findings I have taken into account the matters raised by the paediatric neurologist.

1.15 PHARMAC was given an opportunity to respond to the draft report and provided a written response. I also gave PHARMAC an opportunity to respond to the matters raised by the paediatric neurologist, and a further brief response was submitted. I have taken into account these submissions made by PHARMAC.

1.16 Finally, I have been assisted in my review by Catherine Deans, a senior lawyer who works with me at Claro. Ms Deans has participated in the interviews and has provided valuable assistance with the review generally.

2.0 SUMMARY OF FINDINGS AND RECOMMENDATIONS

Was PHARMAC's decision making process in relation to the sole supply of lamotrigine appropriate?

2.1 With two exceptions, PHARMAC's process in the period leading up to the issuing of its Request for Proposals (**RFP**) for the sole supply of lamotrigine in June 2018 was appropriate. It was evidence based and robust.

2.2 The two exceptions are:

2.2.1 First, PHARMAC ought to have involved its Consumer Advisory Committee (**CAC**) at some point over this period; and, in particular, at some point after the November 2015 Neurological Subcommittee meeting. While it is unlikely that involvement of the CAC would have led to a substantive change in the proposed decision, it was clear that the proposal to move to one brand of lamotrigine would have a significant impact on consumers. The CAC's input would likely have been useful; and involving it would have been good practice.

2.2.2 Secondly, and less significantly, it would have been preferable if PHARMAC had sought further input from its Pharmacological and Therapeutics Advisory Committee (**PTAC**), most likely through PTAC's Subcommittees, at a time closer to the issuing of the RFP in June 2018.

2.3 PHARMAC's RFP and consultation processes were appropriate.

2.4 The PHARMAC Board's decision making process was sound. The Board had sufficient evidence to make the decision on 29 March 2019 to move to one brand of lamotrigine; and this decision was appropriate.

Was the design and execution of PHARMAC's implementation process for the Sole Supply Decision appropriate?

2.5 PHARMAC's implementation process, and risk management strategies, were of a high standard. There are two qualifications to this conclusion:

2.5.1 First, PHARMAC ought to have involved its CAC in the development of its Implementation Plan prior to the Board's decision on 29 March 2019. The CAC was not consulted until June 2019. Given the depth and robust nature of the Implementation Plan, it may be that earlier involvement of the CAC would not have resulted in any significant changes to the Implementation Plan. However, the CAC's consumer voice on the implementation activities and risk mitigation strategies should have been heard earlier in the process.

2.5.2 Secondly, the patient information leaflet was easy to read and, appropriately, encouraged patients to talk to healthcare professionals about the brand change. However, the leaflet did not mention PHARMAC's preparedness to pay the GP's co-payment for patients who wanted to consult their doctor about the change. While that

was mentioned in other places, the patient information leaflet would have been a good place to include this important information for patients.

Given PHARMAC's role in the heath sector, are there areas in which PHARMAC could improve its decision making and implementation processes for brand changes?

2.6 PHARMAC's decision making could be improved by earlier involvement of its CAC. I recommend that PHARMAC continues with the current process of reviewing the CAC and its role; and in doing so takes into account the matters referred to in this report.

2.7 While PHARMAC's implementation activities and risk mitigation strategies were of a high standard, PHARMAC will need to be hyper-vigilant in any future, proposed brand changes involving anti-epileptic drugs (AEDs) – including working as closely as possible with key stakeholders, other agencies, and consumer groups. The role played by the media in reporting on brand switches is significant; and it may be that there is work PHARMAC can do with the media to ensure there is good understanding of the basis of decision making.

3.0 LAMOTRIGINE, BIOEQUIVALENCE, AND INTERCHANGEABILTY

3.1 Prior to the Sole Supply Decision, PHARMAC funded three brands of lamotrigine: Lamictal (supplied by GSK), Arrow-Lamotrigine (supplied by Teva), and Logem (supplied by Mylan).

3.2 Lamictal is the 'innovator' brand. It was being taken by 62% of patients taking lamotrigine. Arrow-Lamotrigine was being taken by 26% of patients; and Logem was being taken by 12% of patients.

3.3 Medsafe approved Logem in September 2016. Logem was first listed on the Pharmaceutical Schedule on 1 June 2018.

3.4 The issues relating to brand changes in medications are not new and have been extensively discussed in New Zealand and internationally. The scientific discipline and clinical specialty that involves all aspects of the relationship between drugs and humans, and the quality use of medicines, is clinical pharmacology. The brief overview that follows in this section is taken from A/Prof Doogue's advice, which is set out in full as **Appendix 2.**

3.5 The concept of **bioequivalence** is important to understanding the Sole Supply Decision. A/Prof Doogue refers to bioequivalence as *"taking one brand of a medicine gives the same amount of drug in the body as taking another".* Two brands of the same medicine are bioequivalent when the same dose gives the same concentration of medicine in people taking the medicine. If the two brands are bioequivalent, then *"the same dose is expected to produce the same clinical effect regardless of which brand is used".*

3.6 Any new brand must demonstrate bioequivalence to the existing (reference) brand. The reference brand is usually the 'originator' (or innovator) brand. Medsafe is the regulator in New Zealand responsible for establishing that generic medicines are bioequivalent to the originator brand.

3.7 **Interchangeability** means that two brands are expected to produce the same results when consistently used. Interchangeability is regulated by Medsafe.

3.8 **Substitutability** means that two brands can be switched. Substitution is undertaken at pharmacies. A/Prof Doogue advises that usual practice in New Zealand is for pharmacies to continue the same brand where possible, especially for narrow therapeutic index drugs; but that brand substitution is permitted. Prior to moving to Logem as the sole brand, substitution between the three funded brands of lamotrigine could occur at the pharmacy level (if, for example, the pharmacy had no stock of one brand).

3.9 The potential risks associated with interchangeability and substitution include patient confusion due to changes in packaging or tablet appearance, and patients having pre-existing preferences for brands which can affect confidence and adherence to regimens, and may result in placebo/nocebo effects (i.e. some of the effects of the medicine might be due to non-pharmacological factors which are affected by expectations and beliefs). These risks can be mitigated, but not eliminated, by patient counselling at the time of brand switching.

3.10 In the case of lamotrigine, bioequivalence between Logem and Lamictal (the originator/innovator brand) was established prior to Logem being distributed for use in New Zealand. In December 2019, after reports of issues after switching brands were raised, Medsafe reaffirmed the bioequivalence between Logem and Lamictal. A/Prof Doogue advises that because lamotrigine brand changes have previously been associated with uncertainty, differences (or not) between brands of lamotrigine have been more thoroughly studied than for most medicines.

3.11 A/Prof Doogue refers to the 'social risks' of brand change. Specifically, he refers to:

a. Change in adherence, confusion, and consequently not taking the medicine in the same way causing a difference in drug effects;

b. A change in placebo/nocebo effect; and

c. Events occurring regardless of the brand change; and that any event occurring soon after a change may be attributed to the change.

3.12 A/Prof Doogue advises that, for reasons not well understood, patients with epilepsy report issues with brand changes more than are reported with brand changes for most other conditions. A characteristic of epilepsy is that seizures are dramatic, intermittent events that fluctuate in frequency. Changes to epilepsy control occur, and are not always easy to explain.

4.0 DECISION MAKING BY PHARMAC – GENERAL APPROACH AND PRINCIPLES

4.1 Before considering the Sole Supply Decision, it is useful to summarise PHARMAC's general approach to making decisions about the funding of medicines. This is not intended as an exhaustive summary of either PHARMAC's processes or its obligations. The focus is on matters most relevant to the Sole Supply Decision (the details of which are considered in the next section).

PHARMAC's Objectives and Factors for Consideration

4.2 PHARMAC's objectives and functions are set out in ss 47 and 48 of the New Zealand Public Health and Disability Act 2000 (**NZPHDA**). At the heart of PHARMAC's objectives is prioritising which medicines will deliver the best outcomes for New Zealanders within the amount of funding provided.

4.3 The consideration of applications for new medicines to be funded, the possibility of moving from innovator medicines to generics and/or from multiple brands to one brand, and the financial implications of such decisions, are core business for PHARMAC. PHARMAC carries out approximately 60 brand changes per year. There is a limited pool of public funds for medicines in New Zealand. Savings in one area lead to availability in another area. Therefore the financial implications are, rightly, at the centre of PHARMAC decision-making – but, it is by no means the only consideration. To assist with its decision making, PHARMAC has established a framework *The Factors for Consideration*.[3] The four main factors for consideration are:

Need – considering the impact of the disease, condition or illness on the person, their family or whānau, wider society, and the broader New Zealand health system.

Health benefit – the potential health gain from the medicine being considered.

Costs and savings – to the person, their family or whānau, and to wider society.

Suitability – the non-clinical features of the medicine that might impact on health outcomes.

PHARMAC's Board and Statutory Committees

4.4 The NZPHDA requires PHARMAC's Board to establish two advisory committees:[4]

a. A Pharmacological and Therapeutics Advisory Committee (**PTAC**). The PTAC's role is *"to provide objective advice to Pharmac on pharmaceuticals and their benefits";*[5] and

b. A Consumer Advisory Committee (**CAC**). The CAC's role is *"to provide input from a consumer or patient point of view".*[6]

[3] *The Factors for Consideration* document is available at https://www.pharmac.govt.nz/medicines/how-medicines-are-funded/factors-for-consideration
[4] NZPHDA, s 50(1)
[5] NZPHDA, s 50(1)(a)
[6] NZPHDA, s 50(1)(b)

4.5 The status of PTAC and CAC as statutory committees emphasises the importance of each committee's role in PHARMAC's decision making. But, both committees are expressly advisory. Decision making ultimately rests with PHARMAC, either through its Board or, under the Board's delegation, by others.

4.6 **PTAC** is a committee of senior health practitioners from multiple specialities selected for their expertise in critical appraisal as well as broad experience and knowledge of pharmaceuticals and their therapeutic indications.[7] PTAC meetings are normally held in Wellington four times per year – but PTAC also meet by teleconference and make recommendations by email.[8]

4.7 PHARMAC has appointed a number of PTAC Subcommittees to provide advice either directly to PHARMAC or to it through PTAC.[9] Of particular relevance for immediate purposes are PTAC's Neurological Subcommittee and its Mental Health Subcommittee.

4.8 PTAC and its Subcommittees are an important part of PHARMAC's decision making. Relevant principles relating to PTAC, its Subcommittees, and PHARMAC include:

a. PTAC may seek advice from Subcommittees on specific issues. Subcommittees give a written opinion to PTAC by way of Subcommittee meeting minutes.[10] Subcommittee minutes are formally reviewed by PTAC at its next meeting.[11] The relevant portions of any PTAC minutes are then provided to each Subcommittee for information and interest.[12]

b. PHARMAC's Medical Director (or delegate) may attend each PTAC and Subcommittee meeting and participate in the discussions.[13]

c. The advice given by PTAC and its Subcommittees is published on PHARMAC's website.[14]

4.9 PHARMAC's Terms of Reference for its **CAC** describes the purpose of the CAC in the following terms:[15]

> The primary purpose of the CAC as described in the legislation is to provide the Board of PHARMAC with input from a consumer or patient point of view on matters relating to PHARMAC's activities. Recognising the difficulties representing the wide range of disparate views held by consumers, it is not intended that the CAC represent all consumer views. The CAC's primary functions, therefore, are to provide advice to PHARMAC on how it can best access the diversity of consumer views and consider these when carrying out its role.

The CAC's Terms of Reference go on to state that *"[t]he CAC does not have a role in pharmaceutical funding decisions"*.

[7] *Terms of Reference for PTAC and PTAC Subcommittees* (2016) (**PTAC Terms of Reference**) at [4.1].
[8] PTAC Terms of Reference at [8.1].
[9] PTAC Terms of Reference at [1.2].
[10] PTAC Terms of Reference at [3.2.1]
[11] PTAC Terms of Reference at [3.2.2].
[12] PTAC Terms of Reference at [3.2.3].
[13] PTAC Terms of Reference at [3.3.1].
[14] PTAC Terms of Reference at [9.4]. This is subject to any specific content being withheld under one of the grounds in the Official Information Act 1982.
[15] *Terms of Reference for the PHARMAC Consumer Advisory Committee* (2010) (**CAC Terms of Reference**) at [2.1].

4.10 PHARMAC describes the CAC's activities as including (but not being restricted to) providing advice to PHARMAC from a consumer or patient point of view on:[16]

- how PHARMAC can canvass and consider consumers' views on the processes involved in the assessment, prioritisation and funding of medicines and related issues of special concern to consumers and patients;
- PHARMAC's strategy, policy and operational activities which relate to funding decisions, and access to and optimal use of medicines, but not specific funding decisions; and
- how PHARMAC's implementation of its funding decisions, policies and strategies, including how information and education related to those funding decisions, policies and strategies would be best communicated to consumers.

4.11 CAC meetings are normally held in Wellington, no less than twice a year. The CAC may also meet by teleconference or provide advice in other ways.[17] Minutes of each CAC meeting are provided to the PHARMAC Board.[18]

Consultation

4.12 PHARMAC has an express, statutory obligation to consult in implementing its objectives and carrying out its functions. When it considers it appropriate to do so, PHARMAC must:[19]

a. consult on matters that relate to the management of pharmaceutical expenditure with any sections of the public, groups, or individuals that, in PHARMAC's view, may be affected by decisions on those matters; and

b. take measures to inform the public, groups, and individuals of PHARMAC's decisions concerning the Pharmaceutical Schedule.

[16] See CAC Terms of Reference at [2.2] for a full list of the activities and how they are described.
[17] CAC Terms of Reference at [10.1].
[18] CAC Terms of Reference at [3.1.2].
[19] NZPHDA, s 49.

5.0 THE SOLE SUPPLY DECISION – THE DECISION MAKING PROCESS

5.1 The Sole Supply Decision was made by PHARMAC's Board at its meeting on 29 March 2019. The documentation before the Board demonstrates that the March 2019 decision was the culmination of a decision making process that could be traced back at least 12 years to 2007.

5.2 In order to properly understand the Sole Supply Decision, it is necessary to traverse the key steps in the decision making process. At the end of each section in the chronology of events that follows, and where it is appropriate to do so, I will add my own comments which will help elucidate the matters which I consider to be of particular significance to my findings.

2007 Neurological Subcommittee Meeting

5.3 On 19 April 2007 the Neurological Subcommittee of PTAC met and undertook a Therapeutic Group Review of Antiepilepsy Drugs (**AED**s). The Subcommittee's Minutes record that the Subcommittee considered that *"patients stabilised on one brand of lamotrigine should not switch brands".*[20]

5.4 The Subcommittee also discussed the rules around 'brand switching' at the pharmacy level. The Subcommittee considered that it would be helpful if PHARMAC could clarify the rules around brand switching – and recommended that PHARMAC staff send out a reminder letter to prescribers explaining the substitution rules.[21]

5.5 The Subcommittee's Minutes were noted and accepted by PTAC, without further comment, at PTAC's meeting in August 2007.

2009 Neurological Subcommittee meeting

5.6 On 2 April 2009 the Neurological Subcommittee met and conducted a further Therapeutic Group Review of AEDs.

5.7 While the Subcommittee's Minutes do not record any specific discussion about lamotrigine, there is record of the Subcommittee's consideration of a possible brand change of another AED, sodium valproate. The Subcommittee acknowledged the particular significance of reduced therapeutic benefit in patients with epilepsy – in particular because of the requirement in New Zealand that patients cannot drive for up to 12 months following a seizure. For this and other reasons the Subcommittee *"was not supportive of any arrangement where patients with epilepsy stabilised on one brand of sodium valproate would be required to switch to a different brand".* The Subcommittee left the door open to the possibility of supporting an arrangement where there may be only one brand funded for new patients – provided certain safeguards were in place.[22]

5.8 The Subcommittee's Minutes were noted and accepted by PTAC, without further comment, at PTAC's meeting in May 2009.

[20] Record of the Neurological Subcommittee of PTAC meeting, 19 April 2007, at [4.12].
[21] Record of the Neurological Subcommittee of PTAC meeting, 19 April 2007, at [4.13].
[22] Record of the Neurological Subcommittee of PTAC meeting, 2 April 2009, at [4.3].

5.9 It is clear to me that in April 2009 the Neurological Subcommittee was, at the least, cautious and conservative when it came to requiring stabilised patients to switch between brands of AED.

2010 Neurological Subcommittee meeting

5.10 The Subcommittee considered AEDs again at its 5 August 2010 meeting. Although, again, referring to sodium valproate (rather than lamotrigine), the following entry in the Minutes is relevant:[23]

> The Subcommittee expressed its concern around the high expenditure on sodium valproate and reiterated its previous comments that it would be supportive of an arrangement where a (cheaper) generic brand would be the only brand funded for new patients, providing that existing seizure-free patients with epilepsy could continue to access their current brand and that there was a period of time in which both brands would be funded for all patients in order for clinicians to become familiar with the new product. The Subcommittee also reiterated its view that the consequences of reduced therapeutic benefit in patients with epilepsy were substantial compared to some other disorders, in particular because of the requirement in New Zealand that patients cannot drive for up to 12 months following a seizure, meaning that the impact of even a single seizure can be significant for patients.

5.11 The Minutes record PHARMAC staff having advised the Subcommittee that they were exploring different options for achieving savings in the epilepsy market.

5.12 The Subcommittee's Minutes were noted and accepted by PTAC, without further comment, at PTAC's meeting in November 2010.

5.13 The Subcommittee's Minutes, and the consideration of these Minutes by PTAC, are a record of the on-going consideration that PHARMAC (including its committees) was giving to AEDs and the implications for moving to one funded brand. From the passage taken from the Minutes set out above, it is clear that the Subcommittee was open to the possibility of moving to one funded brand for new patients – provided safeguards were in place. Further, the Subcommittee was cognisant of the impact on patients – particularly because of the driving restrictions on those who suffer seizures.

2012 Neurological Subcommittee meeting

5.14 At its meeting on 24 July 2012, the Subcommittee considered brand switching of AEDs. After referencing the medical literature, the Subcommittee noted that it considered *"the risk of switching brands"* to be *"low"*. Despite this, the Subcommittee considered that *"insufficient evidence has been reviewed to date to establish the safety of brand switching for patients with epilepsy".*[24] The Subcommittee noted that there are potentially greater risks associated with switching between generic products compared with switching between the innovator brand and a generic brand.[25]

[23] Record of the Neurological Subcommittee of PTAC meeting, 5 August 2010, at [5.2].
[24] Record of the Neurological Subcommittee of PTAC meeting, 24 July 2012, at [3.2].
[25] Record of the Neurological Subcommittee of PTAC meeting, 24 July 2012, at [3.3].

5.15 The Subcommittee's Minutes in relation to AED and brand switching were noted and accepted by PTAC, without further comment, at PTAC's meeting in November 2012.

5.16 It is clear that in 2012 the Subcommittee, and PTAC, continued to take a cautious and conservative approach.

2013 PTAC meeting

5.17 At its meeting on 1 and 2 August 2013, PTAC reviewed a request for advice on the acceptability of switching from the innovator brand of sodium valproate to a generic sodium valproate. The Minutes record PTAC's recommendation that generic sodium valproate should not be listed as 'sole supply' in the Pharmaceutical Schedule.[26]

5.18 The Minutes record that it is Medsafe's role to determine the safety, efficacy and bioequivalence of medicines. PTAC's role was to consider suitability of sole supply.

5.19 The important point for immediate purposes is that in 2013 PTAC gave careful and detailed consideration to the issues relating to brand switching of AEDs, and concluded, at that time, that mandatory switching would not be appropriate. PTAC's Minutes record a detailed discussion, including traversing the medical literature and international standards, on the issues relevant to brand switching of AEDs.

2015 Neurological Subcommittee meeting

5.20 On 11 November 2015, the Neurological Subcommittee met and considered the issue of brand switching of AEDs. This included, for the first time in any specific detail, brand switching of lamotrigine.[27]

5.21 It is relevant to note that the Chair of the Neurological Subcommittee in November 2015, and at the meeting, was Professor Mark Weatherall. Prof. Weatherall was also a PTAC member – and subsequently chair of PTAC, a position he continues to hold.

5.22 The Minutes record a detailed discussion and review of the medical literature. An analysis of the literature and the clinical studies and the, at times, differing conclusions reached, is beyond the scope of this review. However, it is worthy of note that, following its review of the published evidence that included systematic reviews regarding AED brand switching, the Subcommittee concluded that:[28]

> in general, evidence from the randomised controlled trials did not appear to suggest that switching brands of AEDs has an effect on seizure frequency; however, some of the small non-experimental cohort studies reported high switch back rates and increase in health resources in patients who switched.

5.23 For reasons that will become apparent, it is also worthy of note that the Subcommittee gave careful consideration to the AED categorisation system implemented in the United Kingdom by

[26] Record of the PTAC meeting, 1 & 2 August 2013.
[27] Record of the Neurological Subcommittee of PTAC meeting, 11 November 2015.
[28] Record of the Neurological Subcommittee of PTAC meeting, 11 November 2015, at [7.7].

the Medicines & Healthcare products Regulatory Agency (MHRA).[29] The MHRA categorises AEDs to help healthcare professionals decide whether it is necessary to maintain a patient on a specific manufacturer's product. Category 1 involves AEDs where the advice is to maintain the patient on a specific product. Category 2 involves AEDs where the need for continued supply on a particular product is a matter of clinical judgement for the prescriber and involves consultation with the patient and/or the carer. Category 3 relates to AEDs where it is "usually unnecessary" to ensure patients are maintained on a specific manufacturer's product.

5.24 In the UK, the MHRA places lamotrigine in 'category 2'. Relevantly, the Neurological Subcommittee at its November 2015 meeting was unable to come to a consensus in relation to lamotrigine; and *"whether it should be in category one or two, or in category two or three".*[30]

5.25 Despite the lack of consensus on where lamotrigine fits within the UK categories, the Subcommittee reached some important conclusions at this meeting. It is clear from the Minutes that these were conclusions reached after careful consideration of the medical literature and other relevant standards – and were conclusions that came following consideration, over many years, of issues relating to brand switching of AEDs.

5.26 The conclusions reached by the Subcommittee formed the basis of the Sole Supply Decision. The key conclusions warrant specific mention here. The Subcommittee:[31]

a. considered that a managed brand switch to one brand of lamotrigine would be preferable to having multiple brands listed (as was currently the case);

b. considered a competitive process for one brand (sole supply) of lamotrigine would be appropriate *"provided that a suitable transition period was available"*. The Subcommittee considered a transition period of 3-6 months would be required to support any brand switch. Where patients were unable to transition to a new brand for 'exceptional clinical reasons', patients could be considered through PHARMAC's exceptional circumstances pathway;

c. noted that patients are generally averse to change, and that if there is a managed brand switch, any change in seizure frequency could be perceived to have been caused by a change in brand;

d. considered that there were no blood tests that would be useful to assist with monitoring a brand switch for lamotrigine;

e. emphasised the importance of health professionals providing support and reassurance around brand changes and considered that the most important factor for maintaining epilepsy control was medication adherence;

f. considered that GPs and pharmacists would be the health professionals most likely to be involved in supporting a brand change for lamotrigine (should this occur); and

[29] Record of the Neurological Subcommittee of PTAC meeting, 11 November 2015, at [7.10].
[30] Record of the Neurological Subcommittee of PTAC meeting, 11 November 2015, at [7.12].
[31] Record of the Neurological Subcommittee of PTAC meeting, 11 November 2015, at [7.20] – [7.28].

g. noted the New Zealand Transport Agency (**NZTA**) guidance that driving should cease if an individual is having seizures or has had a seizure in the last 12 months. The Subcommittee considered that if a patient were to have a seizure after a brand switch, their physician may be likely to report to the NZTA that they have had a change in brand of medicine by way of explanation. Therefore, the Subcommittee recommended that PHARMAC consult with the Chief Medical Officer of the NZTA should PHARMAC run a competitive process that could result in a managed brand switch for lamotrigine.

5.27 PTAC considered the Neurological Subcommittee's Minutes at its meeting on 11 & 12 February 2016. PTAC noted and accepted the Subcommittee's Minutes without further comment on the possibility of moving to one brand of funded lamotrigine (PTAC commented on other issues raised in the Minutes).

May/June 2016 – PHARMAC's correspondence with NZTA

5.28 On 18 May 2016 PHARMAC wrote to NZTA, through its Chief Medical Advisor, noting the possibility of a managed brand change for some AEDs. PHARMAC provided NZTA with a hyperlink to the Neurological Subcommittee's November 2015 Minutes. PHARMAC proposed a meeting between PHARMAC's Medical Director and NZTA's Chief Medical Advisor to discuss the issue.

5.29 NZTA's Chief Medical Advisor responded by way of letter dated 21 June 2016. The Chief Medical Advisor stated that he was not available to meet, but he provided the following advice to PHARMAC:

> A change to the generic form of the same medication would be seen to be equivalent to a dose change and not a treatment change.
>
> If the difference in bioavailability was thought to be insignificant, then no driving restrictions would be required. If it was thought to be significant then it would be the responsibility of the supplier to warn users of the risks of changing to the new medication, including the driving risks.

2016 Neurological Subcommittee meeting

5.30 On 7 November 2016, the Neurological Subcommittee met and considered, amongst other things, PHARMAC's plan to run a commercial process for one supplier of lamotrigine.

5.31 In the briefing paper provided to the Subcommittee in advance of the meeting, members were reminded of the matters considered at the November 2015 meeting (and provided with a copy of the Minutes of that meeting); and PHARMAC reported to the Subcommittee on the correspondence with NZTA that had been initiated at the suggestion of the Subcommittee. The members were provided with copies of the letters with NZTA referred to above.

5.32 PHARMAC's briefing paper asked the Subcommittee to undertake a 'therapeutic group review' in four areas – one being AEDs. The general questions to the Subcommittee included whether the Subcommittee's review revealed any particular areas of concern; whether there were any

major developments internationally that PHARMAC staff should know about; and whether the Subcommittee had any additional comments relating the therapeutic group review.

5.33 The Minutes for the Subcommittee's meeting record the Subcommittee's position that it could not perceive a problem with having different suppliers for the adult and paediatric strength preparations of lamotrigine tablets. The Minutes also note the correspondence between PHARMAC and NZTA (and record a subsequent meeting between PHARMAC and the NZTA Operations/Policy directorate). That is the extent of the matters recorded in the Minutes.

5.34 The Neurological Subcommittee's Minutes were considered by PTAC at its meeting on 9 and 10 February 2017. PTAC noted and accepted the Minutes with no comments made in relation to the proposal to move to one supplier of lamotrigine.

5.35 It is clear that, by late 2016/early 2017, both the Neurological Subcommittee and PTAC were fully appraised of the steps PHARMAC was taking to run a commercial process for one supplier of lamotrigine. No concerns were raised.

2016 Mental Health Subcommittee meeting

5.36 At the suggestion of the Neurological Subcommittee, the Mental Health Subcommittee of PTAC was asked to undertake a therapeutic group review of lamotrigine and sodium valproate. The reason for this was that these medications are commonly used for mood disorders (in addition to epilepsy).

5.37 The Mental Health Subcommittee met on 23 November 2016. PHARMAC's briefing paper to the Mental Health Subcommittee provided in advance of the meeting informed the Subcommittee about PHARMAC's plans for running a commercial process that could result in only one brand of lamotrigine being funded. The Mental Health Subcommittee members were provided with the Neurological Subcommittee's November 2015 Minutes. PHARMAC posed a number of questions to the Mental Health Subcommittee about the possible brand switch, the transition period, and implementation activities.

5.38 The key conclusion reached by the Mental Health Subcommittee was that:[32]

> it would not be clinically problematic from a mental health standpoint to switch patients from one brand to another if necessary (i.e. no more or less problematic than any other mood stabiliser brand change).

5.39 Other comments made by the Mental Health Subcommittee included:

a. Additional work would be required by pharmacists to reassure patients who were switched brands;

b. Brand switching in the lamotrigine market already occurred, as there are multiple funded brands;

[32] Record of the Mental Health Subcommittee meeting, 23 November 2016.

c. A lamotrigine brand change in patients taking it for mental health indications would be unlikely to require additional clinic visits;

d. A 3-6 month transitionary period appeared to be a sensible implementation timeframe from a mental health perspective;

e. PHARMAC's usual brand switch activities would be sufficient to support a lamotrigine brand change from a mental health perspective; and

f. Because lamotrigine is in its own class amongst mood stabilisers, pharmacologically speaking, some patients may be particularly dependent on it psychologically and may need extra support.

5.40 The Mental Health Subcommittee's Minutes were considered by PTAC at its meeting on 9 and 10 February 2017. PTAC noted and accepted the Minutes with no comments made in relation to the proposal to move to one supplier of lamotrigine.

5.41 It is clear that the Mental Health Committee was fully appraised of the steps PHARMAC was taking to run a commercial process for one supplier of lamotrigine. The Mental Health Committee did not regard the proposal as problematic – and made some useful comments about implementation.

June/July 2018 - Request for Proposals and Provisional Agreement with Mylan

5.42 On 18 June 2018, PHARMAC issued a RFP for the supply of lamotrigine. The RFP noted that since the introduction of generic lamotrigine, PHARMAC had monitored the market and had sought clinical advice on lamotrigine. The RFP noted that the approximate annual expenditure on lamotrigine formulations was $10.2 million. PHARMAC stated that the purpose of the RFP was to obtain the best possible pricing to reduce the total expenditure and secure supply of adult and paediatric lamotrigine through one or two suppliers.

5.43 PHARMAC's Lamotrigine RFP Evaluation Committee selected the proposal submitted by Mylan as the preferred proposal for the supply of the adult presentations of lamotrigine. Mylan's brand of lamotrigine is Logem. Mylan's proposal would deliver savings over $30 million over a five year period.

5.44 In an internal memorandum at the time, PHARMAC noted the following risks of proceeding with Mylan:

a. 89% of patients (approximately 10,700 people) would be required to transition to Logem. While there are multiple brands currently listed, and some patients have switched treatments previously, this would be the first time PHARMAC would have implemented a sole supply approach in this market;

b. There is a risk that if patients suffer adverse effects during the transition that this will be associated with the brand switch;

c. GSK and Teva Pharma may withdraw their paediatric strength lamotrigine from the market; and

d. For each month a decision is delayed, there would be a significant cost in potential savings lost.

August-September 2018 – Consultation process

5.45 PHARMAC's consultation document, setting out the proposal to move to one funded brand of lamotrigine 25 mg, 50 mg and 100 mg tablets (Logem), was released on 29 August 2018. The consultation document was published on PHARMAC's website and was sent, by email, to subscribers to PHARMAC's neurology and mental health distribution lists. It was also sent to PTAC and its relevant Subcommittees, pharmacies and clinicians involved in the treatment of epilepsy and mental health conditions, the Ministry of Health, DHBs, software vendors, suppliers, relevant consumer groups, and other interested parties. Respondents were given four weeks to comment on the proposal.

5.46 The consultation document stated that there would be a three month transition period during which PHARMAC would reduce the subsidy for the other currently funded brands. If the suppliers of those brands did not reduce their price, patients were told that those patients using those brands would need to pay a manufacturer's surcharge for their medicine or change to the fully-funded brand (Logem). After the three month transition period, the Arrow-Lamotrigine and Lamictal brands would be delisted, and patients would need to change to Logem to keep accessing funded lamotrigine. The consultation document stated that prescribers, pharmacists and patients would be supported with information and implementation activities to manage any change.

5.47 The consultation document included hyperlinks that took readers to the clinical advice PHARMAC had received from the Neurological and Mental Health Subcommittees.

5.48 PHARMAC received 32 responses to the consultation – including responses from consumers, health professionals, professional associations, suppliers and others. Generally speaking, consumers, consumer groups and suppliers expressed significant concerns; while health professionals and professional associations were supportive. It is not necessary to set out the different views in any detail here; however, a couple of examples are mentioned to illustrate the range of responses:

a. Dr Charon Lessing, School of Population Health, University of Auckland, submitted in support of the proposal. Dr Lessing referred to her doctoral research into lamotrigine brand switching in New Zealand, and attached her published article on the topic. Dr Lessing's submission noted that her research analysed 1,655 adult New Zealand patients over 12 months post brand switch, with key findings including:

- Approximately one-quarter of patients using the originator brand of lamotrigine switched to generic lamotrigine within 60 days of the policy implementation in 2007.

- For around 10% of those who switched brands, there were multiple switches (three or more) between generic and brand products.
- Switch-back rates of 3% were apparent within 30 days post-switch.
- There was no difference in health outcome measures associated with switching from originator lamotrigine to a generic equivalent.

b. Consumers and consumers groups focussed on the risks seen with brand switching. The consumer submissions were genuine and heartfelt. By way of examples only:

- *"Now I face the horror of another change. I literally feel nauseous having just read about this…I really do appreciate how hard you all have to work to make things work but people will die…"*
- *"In a community which talks to each other, we hear of other people for whom changing brands have triggered seizures."*
- *"As much as your 'experts' will go on about the bioequivalence being the same whatever the brand, you know full well that is not the case in reality because brand switches (of all types of drugs) have a long and clinically proven track record of affecting people individually and there is no guarantee that it won't."*
- One consumer noted, with concern, that the Neurological Subcommittee had not been able to reach a consensus on which (UK MHRA) category lamotrigine fits into – stating that *"without a consensus on this issue people may potentially be given a generic form of medication which may not be suitable for and put them at risk of harm".* This consumer filed a lengthy submission that raised a number of relevant and important points – including about implementation activities.

5.49 The submission made by Medsafe on the proposal warrants particular consideration here. The concerns raised by Medsafe have subsequently attracted media and other attention.

September – November 2018 - Medsafe submission and discussion

5.50 Medsafe is the business unit within the Ministry of Health that is responsible for the regulation of medicines in New Zealand. Medsafe administers the Medicines Act 1981 and associated regulations – and, in doing so, it is Medsafe's role to ensure that medicines meet acceptable standards of safety, quality and efficacy.[33]

5.51 On 19 September 2018 Medsafe made a submission to PHARMAC on the proposal. In its opening paragraph, Medsafe set out its position in the following terms:

> Medsafe considers that the proposal goes against the international consensus on switching between brands of anti-epileptic medicines. Medsafe also considers that this proposal poses a potentially significant safety issue. The international consensus [1] is that even with bioequivalent

[33] See the 'About Medsafe' page on Medsafe's website - https://www.medsafe.govt.nz/other/about.asp.

> anti-epileptic medicines, switching could result in the loss of seizure control for any individual using this medicine to control their epilepsy. A single seizure can be extremely detrimental to a patient's life and all measures should be taken to ensure this risk is minimised. Consensus between international organisations and published literature is that any decision to change brands of AEDs should be made between the prescriber and the patient with approval from a specialist.

5.52 Medsafe's submission commented on specific matters, including the literature, referred to by the Neurological Subcommittee in its Minutes of its November 2015 meeting. Medsafe attached additional publications and studies which Medsafe considered were important.

5.53 On 26 October 2018, PHARMAC announced that it was putting its proposal to move to one funded brand of lamotrigine on hold while it considered the submissions and sought further advice.

5.54 On 13 November 2018, a senior group of PHARMAC representatives met with senior Medsafe representatives to discuss Medsafe's submission. Minutes of the meeting were taken by PHARMAC, with a draft shared with Medsafe – and, in due course, Medsafe marked-up its proposed changes to the minutes.

5.55 Following the meeting, Medsafe wrote to PHARMAC (by way of letter dated 21 November 2018) to clarify its earlier submission. Medsafe raised issues with one of the studies relied on by PHARMAC (Dr Lessing's study, referred to above); and noted that the literature review that PHARMAC relied upon in support of the proposal was conducted three years' previously. Medsafe recommended a further literature review be undertaken. Medsafe also made some recommendations about implementation (should the proposal proceed) – including that the brand switch should not occur when the patient reaches the pharmacy without prior counselling by the GP; and that GPs should refer the most vulnerable patients for specialist intervention to oversee and monitor the switch. Medsafe suggested that easy-to-read leaflets should be prepared and distributed by GPs, specialists and pharmacists – and all patients should be actively followed up to check that they were coping well with the change. Medsafe stated that PHARMAC should ensure that an alternative funding mechanism is made more accessible for patients who need to switch back to their original brand.

5.56 There were other further exchanges between PHARMAC and Medsafe in December 2018 and January 2019. While there were some modifications to Medsafe's position, Medsafe continued to have concerns and maintained its position that lamotrigine should be considered a Category 2 AED under the MHRA categorisation system.

5.57 An important matter on which there was no disagreement between PHARMAC and Medsafe was that all generic brands of lamotrigine approved in New Zealand are all considered bioequivalent to the innovator, Lamictal.

5.58 On 18 December 2018 PHARMAC informed Medsafe that, following Medsafe's feedback and engagement, PHARMAC would be seeking clinical advice from the Neurological and Mental Health Subcommittee. Medsafe were told that the points it had raised would be brought to the Subcommittees' attention; and that an updated literature search would be conducted.

February 2019 – Joint meeting of the Neurological and Mental Health Subcommittees

5.59 On 7 February 2019 a joint meeting of the Neurological and Mental Health Subcommittees was held. The only agenda item for the two Subcommittees was to consider the proposal to switch to one funded brand of lamotrigine.[34]

5.60 A briefing paper was sent to members on 18 January 2019. In accordance with PHARMAC's usual practice, this gave the members three weekends to review the papers in advance of the meeting. The stated purposes of the briefing paper were to seek clinical advice on concerns that were raised during consultation; and to seek clinical advice on possible implementation activities to support the change (should it go ahead). The paper posed a number of questions for the Subcommittees, including the following questions which are central to this review:

- Are the Subcommittee still comfortable with PHARMAC progressing with a move to one funded brand of lamotrigine, supported by the implementation activities noted in this paper and an exceptions mechanism?
- Do the Subcommittees consider that a longer transition (i.e. longer than the previously advised 3-6 months) would be needed to support a brand change should the proposal go ahead?
- Do the Subcommittees have any comments/suggestions regarding the proposed implementation activities noted in this paper?

5.61 The briefing paper provided a comprehensive summary of the consultation feedback (including, but not limited to, Medsafe's concerns, and the communications with Medsafe). A literature search was included, with studies and papers from over 50 publications summarised. A specific section included the publications provided by Medsafe. The paper provided the details of the research that had been undertaken by PHARMAC staff to ensure that all relevant publications were identified. Copies of the publications, consultation responses, and previous Subcommittee minutes were attached as appendices.

5.62 The joint meeting was chaired by Professor Weatherall. There were three other PTAC members in attendance in their capacity as Subcommittee members – meaning that a total of four PTAC members attended. It was an in-person meeting, held in Wellington. The Minutes prepared for the meeting are extensive, and traverse the literature and the Subcommittees' comments on the particular studies. The Subcommittees' summary warrants being set out in full:[35]

> 1.45 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.

[34] There was a second, unrelated agenda item for the Neurological Subcommittee only.
[35] Record of the Joint Neurological and Mental Health Subcommittee Meeting, 7 February 2019, at [1.45] – [1.48]. While the Minutes refer to 'Subcommittee' (in the singular), it is clear that the two Subcommittees were involved.

1.46 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.

1.47 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.

1.48 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.

5.63 It is evident to me from the documentation that I have reviewed that the joint meeting was comprehensive and substantive. All the concerns that had been raised about the proposal were carefully considered. The two Subcommittees' support for the proposal was clear.

29 March 2019 – PHARMAC Board meeting

5.64 PHARMAC's Board considered the proposal to move to one funded brand of lamotrigine at its Board meeting on 29 March 2019.[36] The briefing paper to the Board noted that the proposal had not been dealt with by the Chief Executive under delegated authority because of the estimated financial impact of the proposal and because *"the proposal is considered contentious due to perceived and potential clinical risks of a brand change in this population".*

5.65 The briefing paper provided to the Board canvassed the process PHARMAC had undertaken, including setting out the concerns of Medsafe and other submitters – with the relevant documentation attached to the paper. Subcommittee Minutes were also attached; as was a proposed Implementation plan.

5.66 The briefing paper proposed that implementation would occur over a five month period beginning on 1 May 2019. The Board was informed that, should the proposal be approved, it would mean significant savings of over $30 million over five years to DHBs.

5.67 PHARMAC's Board resolved to move to one funded brand of lamotrigine. The specific resolutions included approving the necessary changes to the Pharmaceutical Schedule; approving the provisional agreement with Mylan; and resolving that the consultation process on the proposal was appropriate and no further consultation was required. These resolutions comprised PHARMAC's Sole Supply Decision.

5.68 Professor Weatherall, the PTAC Chair, attended the Board meeting as an observer. As referred to above, Professor Weatherall had been closely involved in the process – including chairing the joint meeting of the Neurological and Mental Health Subcommittee meeting in February 2019.

[36] The Board had been informed in May 2018 about the intention to initiate an RFP for lamotrigine. PHARMAC told me that the Board was updated on developments at each meeting leading up to the 29 March 2019 meeting.

5.69 The Board's Minutes also record that David Lui, the CAC Chair, attended the Board meeting as an observer. This is the first reference that I have seen in the documentation relating to PHARMAC's decision making process to either Mr Lui, or the CAC. Further comment is made on this below.

Clinical Advisor's advice

5.70 This is an appropriate place to record the advice I have received from A/Prof Doogue on the decision to move to one funded brand of lamotrigine. As I have mentioned, A/Prof Doogue's full advice is attached as **Appendix 2**.

5.71 A/Prof Doogue's key conclusions can be summarised here as follows:

a. PHARMAC could reasonably conclude that for patients who take their medicines correctly, switching between brands of lamotrigine would not cause meaningful differences in drug exposure. PHARMAC could reasonably conclude the pharmacological effects of the brands would be the same.

b. There were no material pharmacological risks with this brand change. The evidence that no pharmacological consequences were expected from the lamotrigine brand change *"was stronger than for almost any other brand change".*

c. PHARMAC had sufficient evidence to conclude that moving to one brand of lamotrigine was appropriate.

d. The conclusions reached by the Neurological and Mental Health Subcommittees at the joint meeting on 7 February 2019 were consistent with, and supported by, the evidence relied on by A/Prof Doogue.

e. A/Prof Doogue does not see any significance in the Neurological Subcommittee's inability to reach a consensus as to whether lamotrigine should be in category 1, 2 or 3 of the UK's MHRA categorisation.

f. PHARMAC's original 'exceptional circumstances' criteria was adequate protection for the particular consumer group.

5.72 In the introduction to this report I referred to my discussions and correspondence with a paediatric neurologist. These took place in early May 2020, which was after I had submitted my draft report to PHARMAC. The paediatric neurologist raised concerns about the prescribing of generic lamotrigine and about PHARMAC's implementation policies. After having read further, publicly available, documents relevant to the issue, some of the paediatric neurologist's initial concerns were alleviated - but the paediatric neurologist continued to express concern as to whether Logem is therapeutically equivalent to the originator brand. The paediatric neurologist also raised concerns about what they regarded as a lack of systematic monitoring, amongst agencies, of treatment failures with generic medicines.

5.73 I have discussed the paediatric neurologist's concerns with A/Prof Doogue and he has reviewed the submissions made by the paediatric neurologist. A/Prof Doogue's advice to me is that the matters raised by the paediatric neurologist do not change his earlier, written advice.

6.0 IMPLEMENTATION OF THE SOLE SUPPLY DECISION

6.1 In order to draw conclusions on the design and execution of PHARMAC's implementation process for the Sole Supply Decision it is useful to continue the chronological overview of PHARMAC's process. It is clear from the chronology set out above, that PHARMAC gave considerable thought to implementation issues during the decision-making process leading up to the Sole Supply Decision. That is evident from the Minutes of the Joint Subcommittees' meeting in February 2019, the correspondence with Medsafe, and other documents.

6.2 At the time PHARMAC's Board made the Sole Supply Decision, the Board had before it PHARMAC's implementation plan – set out in documents entitled *Engagement and implementation approach to support the proposal to change brands of lamotrigine* (referred to from this point as the **Implementation Plan**).

6.3 The Implementation Plan set out four 'key mitigation strategies':

a. Strengthening positive relationships with PHARMAC's sector partners. The plan was to work with other agencies to ensure messages were aligned, and to help monitor and manage the impact. The key stakeholders identified were Medsafe, CARM, and NZTA.

b. Supporting health professionals to change their patients' brand of lamotrigine. The importance of prescribers and community pharmacists were identified. The strategy included:

- providing clear information to health professionals about the change; the bioequivalence of Logem to the originator brand of lamotrigine; and activities available to help them support patients;
- paying a brand switch fee paid to community pharmacy in recognition of the additional patient counselling that would be required during the brand change;
- providing a mechanism to remunerate general practices for appointment fees for patients requiring extra counselling and support from their GP to manage their lamotrigine brand change;
- providing a mechanism under PHARMAC's 'exceptional circumstances' framework for prescribers to apply for their patients to remain on their current brand of lamotrigine. This would be for those patients they think would not manage this brand change.

c. Supporting patients through the brand change. It was recognised that some patients would find the brand change challenging. The strategy included:

- developing patient-focussed resources, including website and downloadable information, using language that would make the brand change understandable for patients;

- developing a communications plan to support notifications and respond to any enquiries received about the change – including ensuing PHARMAC's 0800 enquiry line is supported by pharmacists to respond to patient enquiries;
- providing a link on PHARMAC's website to a survey (managed by the University of Auckland) for patients taking lamotrigine to be able to provide feedback about their experience with the brand change;
- supporting research by the University of Auckland on the brand change to assess the impact of different interventions on people's acceptability of this brand change.

d. Supporting consumer organisations to support their members through the brand change. The strategy was to provide Epilepsy NZ, other epilepsy consumer organisations, and organisations working to support people with mental health conditions, with information to provide their members about the brand change. Specific activities included considering providing financial support to Epilepsy NZ with an epilepsy awareness campaign that includes the importance of medication adherence to AEDs; and producing an epilepsy on-line seminar that Epilepsy NZ field officers could access to update their knowledge about the role of AEDs and medication management.

6.4 PHARMAC announced its decision to move to one funded brand of lamotrigine on 11 April 2019. A standalone 'Decision' document was produced, published on the website, and circulated widely. It set out the implementation activities to support the brand change, and drew readers' attention to PHARMAC's website which would set out further details. It recorded that there would be a five month transition period, during which Lamictal and Arrow-Lamotrigine would remain fully-subsidised; but that from 1 October 2019 these two brands would be delisted and Logem would be the only funded brand of lamotrigine 25 mg, 50 mg and 100 mg dispersible tablets.

6.5 On 11 April 2019 PHARMAC representatives had a teleconference with Medsafe representatives to discuss the notification of the change. PHARMAC's file note records that there was discussion about the steps PHARMAC was taking, and intending to take. The file note records that Medsafe's feedback was that the key messages 'look good'.

6.6 Throughout April and May 2019 PHARMAC circulated its decision widely, initially by email to key stakeholders, all recipients of the consultation document, and those who had provided feedback on the consultation process. On 26 April 2019 the Pharmaceutical Schedule update, confirming the change, was sent to 1,023 community pharmacies.[37] On 2 May PHARMAC released a 'News story', which was emailed to 1,197 subscribers to PHARMAC's electronic mailing list. The publication outlined the change; noted the availability of the brand switch fee; and contained a hyperlink for access to a downloadable patient information leaflet.

[37] PHARMAC told me that there are 900 registered pharmacies in New Zealand, and that its subscriber list may include duplicates.

6.7 On 17 May 2019, PHARMAC emailed primary care groups informing them about PHARMAC's preparedness to meet the costs of any GP visit co-payment. The details of the process for seeking reimbursement were provided.

6.8 I note, here, that the downloadable patient information leaflet suggested that patients talk to their healthcare professionals if they had any concerns about changing brands. However, the leaflet did not state that PHARMAC would meet the costs of any GP visit co-payment. PHARMAC told me that, at this time, the reimbursement process had not been developed.

6.9 On 11 June 2019, PHARMAC hosted a Facebook live "Ask me anything" event for consumers to ask about issues relating to the brand switch. The event was prompted by what PHARMAC considered to be significant misinformation circulating on social media, and in particular on Facebook.

6.10 The CAC met on 12 June 2019. The Minutes of this meeting record a number of matters that are relevant for immediate purposes. First, there is reference to the previous CAC meeting that had been held on 6 March 2019. Secondly, the Minutes record that CAC members noted that there were no update papers for this meeting. Thirdly, there is reference to a review of the role of the CAC and how PHARMAC could be more effective in incorporating the consumer voice in its processes. Fourthly, the CAC received a presentation from senior PHARMAC staff on generic medicines and PHARMAC's management of brand changes. The presentation used the current brand change of lamotrigine as an example – with details provided on the steps PHARMAC had taken as part of the implementation of the decision. The Minutes then record the following:

> Members asked about whether support information had been provided to health help lines, and practice nurses, as these tended to be first points of contact for patients?
>
> Staff acknowledged this point, and said they would look into it.

6.11 I will address this point further in the Findings section below. However, I note here, that this is the first record that I have seen of the CAC being given any information about either the proposal to move to one brand of lamotrigine, or the Sole Supply Decision itself, or the implementation strategy. When the CAC was given some details, as an example to illustrate PHARMAC's management of brand changes generally, the CAC members raised a matter that not only appears pertinent, but was something that does not appear to have been directly considered to that point.

6.12 On 21 June 2019, PHARMAC presented to Epilepsy NZ field support officers on the move to one brand of lamotrigine. PHARMAC provided almost $7,000 of funding to Epilepsy NZ to enable field support officers from around the country to attend the Auckland meeting. PHARMAC also arranged for Dr John Mottershead, a University of Otago neurologist and a member of the Neurological Subcommittee of PTAC, to attend and present on lamotrigine and the switch to one brand. PHARMAC representatives provided extensive information to the field support officers on the brand change, including practical information for patients.

6.13 On 9 August 2019, Medsafe informed PHARMAC that there had been four 'brand switch' reports to CARM relating to lamotrigine.

6.14 On 22 August 2019, Best Practice Advocacy Centre (**BPAC**) published its article '*The funded brand of lamotrigine is changing*'. The article was distributed to primary healthcare professionals and relevant specialist groups.

6.15 This is a suitable place to interpose in the chronology and comment further on BPAC's role and PHARMAC' engagement with BPAC. BPAC is an independent New Zealand organisation that delivers educational and continuing professional development programmes to medical practitioners and other health professionals. Separate to the decision making relating to lamotrigine, PHARMAC has, at its own expense, engaged BPAC to develop a series of modules in relation to generic medications. BPAC has produced articles on issues including monitoring brand changes, bioequivalence and bioavailability, and generic medicines.

6.16 Another, more general step PHARMAC has taken in this area is the preparation of an online, e-learning module *Beyond the Brand* (2017). The e-learning module traverses PHARMAC's role, and such issues as brand changes, generic medicines and bioequivalence.

6.17 On 2 September 2019, there was a telephone conference between PHARMAC and the CEO of Epilepsy NZ. This was one of many communications between PHARMAC and Epilepsy NZ during, and following, the transition period in 2019. As on other occasions, the importance of ensuring that media and other reporting did not create undue fear or anxiety for patients was emphasised. On 10 September there was a Zoom meeting between PHARMAC and Epilepsy NZ. It is clear from these, and other, records that PHARMAC was going to considerable lengths to keep open lines of communication with Epilepsy NZ.

6.18 PHARMAC received the first media enquiries about the move to one brand of lamotrigine on 10 September 2019 and, over the following period, a number of media requests were made to PHARMAC.

6.19 Around the same time, media were approaching NZTA. NZTA initially informed the media (RNZ) that *"in light of Medsafe's submission to PHARMAC"* NZTA was reviewing its policy that the brand change was not a change in treatment that required a six month stand down from driving. NZTA subsequently stated that it would not be enforcing a mandatory stand down period from driving; but recommended a voluntary eight week stand down period for those who are changing to Logem from another brand of lamotrigine. NZTA's advice caused concern and confusion amongst health professionals and patients.

6.20 NZTA's advice led directly to Epilepsy NZ writing to the Minister of Health, on 1 October 2019, asking for the Minister to instruct PHARMAC to make Lamictal and Arrow-lamotrigine available to people with epilepsy who are seizure-free and driving.

6.21 PHARMAC convened a teleconference meeting of the Neurological Subcommittee meeting on 8 October 2019 to discuss NZTA's position, the CARM reports, implementation activities, and other issues relating to the brand change. The Subcommittee's Minutes note that members did

not regard it as their role to interpret NZTA's advice. The Minutes record their role as being to provide clinical and evidence based advice to PHARMAC, and their patients. The Minutes state that the brands are bioequivalent and interchangeable and therefore there should be no clinical problem with changing brands. The Subcommittee noted that patients with epilepsy will have seizures and are not at an increased risk due to a brand change.

6.22 PHARMAC continued to keep the Neurological Subcommittee informed as media interest increased throughout October 2019. The Subcommittee members were also informed about the increasing CARM reports – which, by 31 October 2019, had reached 43 since 1 May 2019, including three reported fatalities.

6.23 In PHARMAC's communication with the media over this period, PHARMAC consistently emphasised, and asked the media to emphasise, the important message that people who have been prescribed Logem do not stop taking it – and that if patients have concerns they should contact their doctor, and PHARMAC would reimburse the costs.

6.24 On 6 November 2019, PHARMAC's Acting Medical Director, sent an email to primary care groups and other key stakeholders. The email noted the ability of GPs to claim reimbursement from PHARMAC for patient consultations relating to additional support because of the brand change; informed practitioners about the exceptional circumstances pathway; and provided a hyperlink to the downloadable patient information leaflets. The email also contained a hyperlink to the article prepared by BPAC New Zealand which includes practical advice on the brand change.

6.25 On 12 November 2019, Medsafe issued an alert about suspected adverse reaction reports received by CARM. This included reporting that CARM had received reports of three deaths – but that the cause of death remained unknown. Medsafe's alert triggered further media enquiries.

6.26 On 14 November 2019, PHARMAC decided to widen the access criteria for other brands of lamotrigine under its 'exceptional circumstances' process. On 15 November 2019, by way of letter circulated to primary health providers, PHARMAC's Acting Medical Director advised that PHARMAC would consider funding applications from prescribers who may have difficulty changing brands due to medical reasons or other concerns. This would include individuals that prescribers considered had not tolerated the changes; have had breakthrough seizures; have had mood destabilisation; where there are clinical concerns about the individual's ability to manage the change; or where there are concerns about the ability to drive. PHARMAC provided a hyperlink to further information and the relevant, updated application forms.[38]

6.27 Significant media interest, and reporting, continued throughout November and December 2019 (and in due course into 2020). As at 24 January 2020, CARM had received 191 reports for lamotrigine, of which 170 were brand related.

[38] Both the original application form and the updated application form have been provided by PHARMAC and considered by the reviewer and the clinical advisor.

6.28 As at the end of January 2020, more than 2000 people were confirmed on PHARMAC's 'exceptional circumstances' pathway, which meant that these people were receiving a different brand of lamotrigine than Logem. At that time, PHARMAC continued to receive around 30 applications each day for 'exceptional circumstances' funding.

Clinical Advisor's advice

6.29 A/Prof Doogue's advice is that brand changes are a normal, rather than an unusual, occurrence. Implementation planning, and risk mitigation strategies, are directed at the management/social risks associated with the brand change to Logem.

6.30 In A/Prof Doogue's opinion, the guidance offered by PHARMAC around switching brands *"was sufficient to inform good medicines counselling by doctors, pharmacists and nurses".* He noted that Logem was in existing use in New Zealand. This was not switching all patients from one brand to another; but consolidation to use of a single brand. A/Prof Doogue concluded by stating that:

> In my opinion PHARMAC's implementation planning and risk mitigation was of a high standard. Putting additional resources to this would have added cost and been unlikely to reduce risk.

6.31 Insofar as the response to the adverse reaction notifications is concerned, A/Prof Doogue has advised:

> Following reports of problems, the media reports and the reported statements of some health professionals may have further contributed to the problem. The possibility of problems was foreseen and the reasons for such problems are known. Attributing the cause of the problems to the pharmacological effects of the Logem brand risks diagnostic error and consequent management errors. This possibility cannot be excluded and needs to be investigated but apriori causality is unlikely.

6.32 A/Prof Doogue advised that while the broadening, by PHARMAC, of the 'exceptional circumstances' criteria in November 2019 was an understandable response due to public concern, A/Prof Doogue considers that such broad criteria may not be appropriate in future, similar cases.

7.0 FINDINGS

Was PHARMAC's decision making process in relation to the sole supply of lamotrigine appropriate?

7.1 In this section I will set out my findings on the appropriateness of the decision making process leading up to, and including, PHARMAC's Sole Supply Decision made by its Board on 29 March 2019. My findings on this issue are structured as follows:

a. PHARMAC's consideration of the issues relating to sole supply leading up to the June 2018 RFP;

b. The RFP and subsequent consultation process (including the communications with Medsafe) (i.e. June - December 2018);

c. The joint Subcommittees' meeting and the Board's decision (i.e. January – March 2019).

PHARMAC's consideration of issues leading up to June 2018

7.2 PHARMAC's consideration of moving to one brand of lamotrigine can be readily traced to the 2007 meeting of PTAC's Neurological Subcommittee. The assessment at that time was that patients stabilised on one brand of lamotrigine should not change brands.

7.3 The question of moving to one brand of AEDs was considered further by the Neurological Subcommittee in 2009, 2010, and 2012. The relevant Subcommittee Minutes demonstrate a gradual, but clear, change in position by the Neurological Subcommittee over these years. By 2010, the Subcommittee was expressing its concern about the high cost of another AED, sodium valproate; and was at least open to the possibility of moving to one funded brand for new patients, provided safeguards were in place (including existing seizure-free patients accessing their current brand). By 2012, the Subcommittee considered the risk of switching brands to be low; but considered insufficient evidence had been reviewed to establish the safety of brand switching for patients with epilepsy.

7.4 The Neurological Subcommittee's meeting in November 2015 was a defining moment in PHARMAC's decision making process. There was a detailed discussion and review of the medical literature. Despite the lack of consensus on which category in the UK MHRA categorisation system lamotrigine is in, the Subcommittee reached the clear conclusion that a managed brand switch to one brand of lamotrigine was preferable to having multiple brands listed; and that provided there was a suitable transition period, and good implementation strategies, a competitive process for one brand of lamotrigine would be appropriate.

7.5 The Neurological Subcommittee then gave the matter further consideration in November 2016; when it considered PHARMAC's plan to run a commercial process for one supplier of lamotrigine. Appropriately, the Mental Health Subcommittee also considered the matter and lent its support to the proposal.

7.6 I am satisfied that the Neurological Subcommittee was the proper body, under the broader PHARMAC umbrella, to be carefully scrutinising the medical literature, the international

approaches, and giving clear advice to PHARMAC on the issue of AEDs. This is a multi-disciplinary committee of independent medical specialists, comprising a majority of neurologists, which is well-placed to provide advice to PHARMAC on issues arising from the prescribing of AEDs. It is clear that, over a number of years, the Neurological Subcommittee's position changed – and when the Subcommittee was opposed to any brand switch, the matter was left until there was further reason for it to be reconsidered.

7.7 In my view, PHARMAC's engagement of the Neurological Subcommittee was appropriate and good practice. Further, the decision-making by the Subcommittee itself was evidence-based and appropriate.

7.8 I note that, from his perspective, A/Prof Doogue considered that the Neurological Subcommittee had sufficient evidence to conclude that moving to one brand of lamotrigine was appropriate. I note, too, that A/Prof Doogue did not see the lack of consensus amongst the Subcommittee as to the UK MHRA categorisation of lamotrigine as being significant.

7.9 PHARMAC's decision to put the matter before the Mental Health Subcommittee in November 2016 was also good practice. This meant that another specialist committee, comprising a majority of psychiatrists, also considered the issues insofar as they related to people who use lamotrigine for the treatment of mood disorders.

7.10 As set out earlier, PTAC is the statutory committee whose role is to provide objective advice to PHARMAC on pharmaceuticals and their benefits. Over the relevant period, there was one PTAC meeting (in 2013) where the Minutes record a detailed discussion, including traversing the medical literature and international standards, on the issues relevant to brand switching of AEDs. However, importantly, the Neurological and Mental Health Subcommittees are subcommittees of PTAC, and all the Minutes of the subcommittees are received and considered by PTAC. It is clear that PTAC was fully appraised of the position taken by the Neurological Subcommittee over the years – including the substantive recommendation made by the Neurological Subcommittee in November 2015 and the further consideration by that Subcommittee, and the Mental Health Subcommittee, in November 2016.

7.11 I am satisfied that PTAC maintained an appropriate role over this period, consistent with its statutory purpose.

7.12 The regular and substantive input of PTAC, largely but not only through the Neurological Subcommittee, can be contrasted with the lack of any input from the CAC in the preliminary consideration of the issues leading up to the June 2018 RFP. I have seen no record of the CAC being either informed about, or asked to consider, issues relating to the possibility of moving to one brand of lamotrigine.

7.13 Given the CAC's statutory role is to provide input to PHARMAC from a consumer or patient point of view, and noting the significance of a brand switch of an AED to patients who suffer from epilepsy and mental health conditions, the lack of any input of CAC is surprising.

7.14 I would not have expected to see CAC's involvement going back as far as the involvement of PTAC and its subcommittees. But, I would have expected to see consultation with the CAC at least at some point following the Neurological Subcommittee's November 2015 meeting, and before the June 2018 RFP process. In my view, the CAC should have been asked to contribute to the discussion points that flowed from the recommendations made by the Neurological Subcommittee in November 2015 – such as, for example, the steps to be taken to ensure patients' general aversion to change was well managed; the best means to provide support and reassurance; and the issues relating to NZTA and possible implications for driving.

7.15 Given the clear recommendations made by the Neurological Subcommittee, including the apparently careful consideration given by that Subcommittee to the impact of the proposed move to one brand on consumers, it seems unlikely that the CAC would have taken a position that was substantively inconsistent with the position taken by the Neurological and Mental Health Subcommittees (and PTAC). But that does not mean there was no need to seek the input of CAC before proceeding with the RFP.

7.16 The failure to consult CAC is the principal exception to my finding that PHARMAC's process leading up to the RFP in June 2018 was appropriate.

7.17 There is a second, but less significant, exception. By the time the RFP was issued in June 2018, it was over 2 ½ years since the Neurological Subcommittee had considered, in detail, the medical literature relevant to the proposal to move to one brand of lamotrigine. The Neurological Subcommittee (and the Mental Health Subcommittee) did consider the issue in November 2016, which was an opportunity for members to note any substantive changes in the literature; but that meeting was 20 months prior to the issuing of the RFP. There is no record, after November 2016, of the Neurological Subcommittee members being given an opportunity to note any changes in the literature. In my view it would have been preferable for the Subcommittee members to have been given an opportunity to provide an updated view (and, possibly, to consider an up-to-date literature review) in closer proximity to the issuing of the RFP. I note that Medsafe raised this point with PHARMAC as part of the consultation process (and this, in due course, led to an updated literature review). An up-to-date analysis of the literature closer to June 2018 might have helped satisfy Medsafe, in late 2018, that the proposal was supported by the current evidence.

7.18 Therefore in summary, my findings in relation to PHARMAC's consideration of issues leading up to June 2018 are as follows:

7.18.1 PHARMAC's process in the period leading up to the RFP in June 2018 was appropriate – and indeed evidence based and robust – with two exceptions;

7.18.2 PHARMAC ought to have involved CAC at some point over this period, and in particular at some point after the November 2015 Neurological Subcommittee meeting. However, it is unlikely that involvement of the CAC over this period would have led to a substantive change in what was proposed.

7.18.3 It would have been preferable if PHARMAC had sought further input from PTAC, most likely through its Subcommittee(s), at a time closer to the issuing of the RFP in June 2018.

The RFP and subsequent consultation process

7.19 As discussed earlier, PHARMAC issued the RFP for the supply of lamotrigine on 18 June 2018. Following consideration by the RFP Evaluation Committee, Mylan's proposal was selected as the preferred proposal and PHARMAC moved to negotiating a provisional agreement with Mylan. The documentation suggests that this was an efficient and proper process. From what I have reviewed, I am confident that the RFP process was appropriate.

7.20 I am also satisfied that PHARMAC's consultation process was appropriate. I note the following:

7.20.1 The consultation document was a succinct and easy to read summary of the key points. It included a hyperlink to the advice PHARMAC had received from the Neurological and Mental Health Subcommittees.

7.20.2 The consultation document was available, and circulated, widely. A good number of substantive and thoughtful submissions were received from a cross-section of stakeholders and interested parties.

7.20.3 PHARMAC properly analysed the feedback received and took notice of it. The clearest example of this is that in October 2018 PHARMAC announced that it was putting its proposal on hold while it considered the submissions and sought further advice. In my view, this was the right step for PHARMAC to take at that time, and demonstrates the preparedness of PHARMAC to keep an open mind and properly consider the feedback it had received. This was good, administrative decision making.

7.20.4 Medsafe's submission, rightly, attracted significant attention within PHARMAC. In my view, PHARMAC responded appropriately. Having made the decision to put the proposal on hold, PHARMAC representatives engaged with Medsafe. Medsafe's recommendation that a further, updated literature search be undertaken was accepted – and this led to the joint meeting of the Neurological and Mental Health Subcommittees in February 2019. PHARMAC continued to keep Medsafe informed of developments as matters progressed.

7.20.5 In due course, changes were made to PHARMAC's final decision that can be traced to the consultation feedback. By way of examples, in the consultation document PHARMAC proposed a three month transition period, with PHARMAC stating that during this period, people using the out-going brands would need to pay a surcharge if the supplier did not reduce their price. The final transition period was five months; during which PHARMAC continued to fully-fund the other brands. Again, these changes demonstrate good, administrative decision making.

The joint Subcommittees' meeting and the Board's decision

7.21 PHARMAC's decision to convene a joint meeting of the Neurological and Mental Health Subcommittees in February was good practice. The two Subcommittees were the right groups to consider carefully the updated literature, the concerns raised by Medsafe and other submitters, and to advise PHARMAC whether the proposal to move to one funded brand of lamotrigine should proceed.

7.22 The two Subcommittees were comprehensively briefed in advance of the meeting – including being provided with an extensive body of literature (including the publications identified by Medsafe). The questions put to the Subcommittees were the right questions – including the ultimate question as to whether the Subcommittees were still comfortable with PHARMAC progressing with a move to one funded brand of lamotrigine. PHARMAC was clearly prepared to be told by the Subcommittees that the proposal should not proceed.

7.23 The Minutes of the meeting were comprehensive and substantive. The recommendations were clear – including that the Subcommittees were supportive of the proposal to move to one funded brand of lamotrigine, with appropriate implementation support.

7.24 In my view, this aspect of PHARMAC's decision making process was appropriate.

7.25 As I have mentioned earlier, if a meeting of the kind held in February 2019 (including an analysis of the up to date literature) had been held just prior to the issuing of the RFP in June 2018, it may be that some of the concerns identified by Medsafe in September 2018 might have already been addressed, with Medsafe's feedback being different to that which it submitted. But, given where matters stood in December 2018, PHARMAC's decision to seek advice from the two Subcommittees was the right the course of action to take.

7.26 The joint Subcommittee meeting was on 7 February 2019. The Board met on 29 March 2019. Relevantly, the CAC held a meeting on 6 March 2019. In my view, this was a missed opportunity for the CAC to have been involved in the decision making process and to have provided input to PHARMAC from a consumer or patient point of view prior to the Board making its decision on 29 March 2019.

7.27 The Board's decision making process itself on 29 March 2019 was sound and appropriate. The Board was well briefed, with all relevant information before it. The Board had before it PHARMAC's *Factors for Consideration* framework; and this framework was considered in the context of the lamotrigine decision. The concerns raised by Medsafe and other submitters were set out, and the Board had all the relevant information from the Subcommittees and PTAC. The Board had before it the comprehensive Implementation Plan.

7.28 The decision was referred to the Board due to the contentious nature of it; rather than being made by the Chief Executive under delegation. That was the correct approach to take here.

7.29 In my view, PHARMAC's Board had sufficient evidence to make the decision to move to one brand of lamotrigine; and this decision was appropriate. I note that my conclusion on this is consistent with the advice that I have received from A/Prof Doogue.

Was the design and execution of PHARMAC's implementation process for the Sole Supply Decision appropriate?

7.30 I accept the advice received from A/Prof Doogue that there were no material pharmacological risks associated with the decision to move to one brand of lamotrigine. That is consistent with the position taken by the Subcommittees that there was no pharmacological reason to suggest there would be a clinical problem. It also appears to be consistent with Medsafe's view that all generic brands of lamotrigine approved in New Zealand are considered bioequivalent to the innovator brand.

7.31 I also accept A/Prof Doogue's advice that this means that implementation planning, and risk mitigation strategies, are therefore directed at the management/social risks associated with the brand change. Again, this seems to be consistent with the approach taken by PHARMAC in its development of its Implementation Plan and mitigation strategies. In my view, that was appropriate.

7.32 As discussed above, PHARMAC's Board had an Implementation Plan before it when it made its decision on 29 March 2019. The genesis of that Plan, and in particular the significant non-pharmacological challenges associated with AED brand changes, can be traced back to the early Neurological Subcommittee meetings referred to in this report. The Neurological Subcommittee's Minutes from its November 2015 meeting, in particular, record in some detail the steps that needed to be taken to manage any change in brand of lamotrigine, and the risk mitigation strategies. Implementation activities were raised during the consultation process, with feedback carefully considered by PHARMAC. The joint Subcommittees' meeting in February 2019 addressed the issue.

7.33 In my view, PHARMAC's recognition of the importance of robust implementation activities is evident throughout the entire decision making process.

7.34 PHARMAC's four 'key mitigation strategies' in its Implementation Plan were borne out of the decision making process. The focus was on strengthening positive relationships with PHARMAC's sector partners; supporting health professionals to change their patients' brand of lamotrigine; supporting patients through the brand change; and supporting consumer organisations to support their members through the brand change.

7.35 I have set out above the specific steps that PHARMAC took to execute the Implementation Plan; and it is not necessary to repeat all the details here. However, I note the communications with health professionals; the preparation of a patient information leaflet; the engagement of BPAC; the hosting of a Facebook live session; and the efforts put in to presenting to Epilepsy NZ field support officers (including the funding provided to Epilepsy NZ for this).

7.36 I accept A/Prof Doogue's advice that the guidance offered by PHARMAC around switching brands was sufficient to inform good medicines counselling by doctors, pharmacists and nurses. I also accept, with two qualifications, A/Prof Doogue's opinion that PHARMAC's implementation and risk mitigation were of a high standard.

7.37 My first, and principal, qualification to this conclusion relates, again, to the CAC. A/Prof Doogue was not asked to comment on the role of the CAC.

7.38 In my view, the CAC's input on the Implementation Plan should have been sought by PHARMAC well before it was sought on 12 June 2019 as part of a general briefing and presentation on PHARMAC's management of brand changes. While there was still time, in June 2019, for the CAC to make useful contributions relevant to implementation of the Sole Supply Decision, by then it was almost three months since the Board had made the decision, and the execution of the Implementation Plan was well advanced. As I mentioned earlier, it is revealing that the Minutes of CAC's 12 June 2019 meeting record the CAC members suggesting an action that does not appear to have been considered, to that point, by PHARMAC – that being, whether support information had been provided to health helplines and practice nurses, with these tending to be first points of contact for patients.

7.39 In my view, PHARMAC's design and execution of the implementation process was appropriate. But, PHARMAC ought to have involved its CAC in the development of its Implementation Plan prior to the Board's decision on 29 March 2019. Given the depth and robust nature of the Implementation Plan, it may be that earlier involvement of the CAC would not have resulted in any significant changes to the Implementation Plan. However, the consumer voice needs to be heard earlier in the process.

7.40 The second qualification to the conclusion that PHARMAC's implementation and risk mitigation were of a high standard relates to the patient information leaflet mentioned earlier. I understand that PHARMAC had not developed the reimbursement process at the time the leaflet was commissioned. But, it would have been preferable if the sequence of events had allowed for the leaflet to mention PHARMAC's preparedness to pay the GP's co-payment for patients who wanted to consult their doctor about the change. While that was mentioned in other places, the patient information leaflet would have been a good place to include this important information for patients.

7.41 The matters that arose between September and December 2019, including the media enquiries and reports, were clearly challenging for PHARMAC. My view is that PHARMAC appropriately managed this difficult period. It was open and transparent with the media – and continued to emphasise the key messages around the need for patients to continue to take medication and seek advice from health professionals. There was continuing dialogue with Medsafe, NZTA, Epilepsy NZ and others. PHARMAC initiated contact with the Office of the Chief Coroner to offer its full cooperation in any inquiries.

7.42 There is one specific matter that warrants further comment. As described earlier, on 14 November 2019 PHARMAC decided to broaden its 'exceptional circumstances' criteria for

accessing funding for other brands of lamotrigine. That was a decision that needs to be reviewed in the context in which it was made. The context being, there were increasing media reports about adverse reactions, which in turn were leading to significant alarm amongst consumers; as well as NZTA's advice around driving which was causing concern. Whether evidence-based or not, there was a real likelihood that patients would stop taking Logem, which would likely have severe implications for the patients. Rightly or wrongly, consumer confidence in Logem was diminishing. In my view, PHARMAC made the right decision by broadening the exceptional circumstances criteria.

7.43 I acknowledge A/Prof Doogue's comments that such broad criteria might not be appropriate in future, similar circumstances. There may well be work that PHARMAC can do to ensure that, if similar circumstances arise in the future, there is less likely to be the need to broaden the exceptional circumstances criteria. However, I do not regard the decision in November 2019 as setting any sort of precedent for future decisions. The November 2019 decision to broaden the exceptional circumstances criteria was unique. It was particular to its own set of facts and the context in which the need to make the decision arose.

Given PHARMAC's role in the health sector, are there areas in which PHARMAC could improve its decision making and implementation processes for future brand changes?

7.44 It will be clear from the findings set out above that, in the main, I have reached the view that PHARMAC's decision making and implementation processes were appropriate. In fact, other than in respect of the matters I have mentioned, my view is that PHARMAC's decision making and implementation processes were of a high standard.

7.45 I have set out my findings in relation to the minimal involvement of the CAC and I do not need to repeat those findings. It will be clear that, in my view, PHARMAC's decision making could be improved by much earlier involvement of its CAC.

7.46 I do want to emphasise the point that involvement of consumers in decision making of the kind PHARMAC is routinely undertaking must not be token. I am not suggesting, here, that PHARMAC's approach to involving consumers is token. In fact, to the contrary, I was reassured to hear that PHARMAC's Board is particularly encouraging of consumer involvement; and I was also reassured to hear that there is active consideration being given to the best way to utilise the CAC in decision making.

7.47 Consumer involvement in health sector decision making is now commonplace. Consumers play an active role in decision making on matters relating to regulation of health professionals, complaint investigations, credentialing, ethical decisions, and DHB decision making (amongst other things). There are many examples of consumer representatives sitting alongside health professionals and contributing, substantively, to decision making.

7.48 Consumers have a particular voice in PHARMAC's decision making through the statutory CAC. It is beyond the scope of this review to undertake a detailed analysis of the role of the CAC. However, it has attracted my attention that the CAC's Terms of Reference state that the CAC *"does <u>not</u> have a role in pharmaceutical decision making"*; and that CAC's role is to provide

advice to PHARMAC on how it can *"best access the diversity of consumer views*" (my emphasis). As part of its review of the role of CAC, I recommend that PHARMAC gives some thought as to how these descriptions fit with the CAC statutory role (as set out in s 50(1)(b) NZPHDA); and whether PHARMAC's decision making might be improved by encouraging the CAC to play a more substantive role in decision making.

7.49 Therefore my principal recommendation is that PHARMAC continues with the current process of reviewing the CAC and its role; and in doing so takes into account the matters referred to in this report. In particular, I recommend that PHARMAC considers involving the CAC earlier in the decision making process and encouraging the CAC to play a more substantive role in decision making (albeit, like PTAC, as an advisory committee).

7.50 This decision making process, and its implementation, has highlighted the particular sensitivities around brand changes for AEDs. As I have said, my view is that PHARMAC's implementation activities and risk mitigation strategies were generally of a high standard. However, it is clear that PHARMAC will need to be hyper-vigilant in any future, proposed, AED brand switches – including working as closely as possible with key stakeholders, other agencies, and consumer groups. The role played by the media in reporting on such brand switches is significant, and it may be that there is work PHARMAC can do with the media to ensure there is good understanding of the basis for decision making.

Appendix 1 – Terms of Reference

Terms of Reference for the Independent Review of PHARMAC's Lamotrigine Sole Supply Decision

Background:

On 11 April 2019 PHARMAC decided to award sole supply of the drug lamotrigine to a single brand, Logem, supplied by Mylan (the "**sole supply decision**"). [39] Previously, three brands of lamotrigine had been funded, including Logem. Lamotrigine is an anticonvulsant predominantly used for the treatment of epilepsy and some mental health conditions.

The decision meant that approximately 11,000 people would need to change the brand they use in order to continue receiving funded lamotrigine. Logem became the only funded brand from 1 October 2019 following a five month transition period. PHARMAC adopted a range of measures to support the implementation of the sole supply decision.

PHARMAC received a range of advice and feedback prior to making the sole supply decision. This included advice from its expert neurological and mental health subcommittees, from Medsafe (the medicines regulator), and from many other parties. A considerable amount of feedback was received via a public consultation process which commenced in August 2018. There were a range of conflicting views as to whether the proposal should proceed.

On 12 November 2019 Medsafe issued a monitoring communication concerning suspected adverse reaction reports in relation to lamotrigine which included (at that time) three deaths. Those deaths have been referred to the Coroner.

On 15 November 2019 PHARMAC announced that it was widening the criteria for its exceptional circumstances to make it easier for patients to remain on their current brand of lamotrigine where their doctor believed it was right for them.

Purpose of the review:

The Independent Review has been established to:

- Provide an independent view on whether the decision making and implementation processes followed by PHARMAC in relation to the sole supply decision were appropriate, and

- To identify any areas in which PHARMAC could improve its decision making and implementation processes for any future brand changes.

[39] The decision related to the 25mg, 50mg, and 100mg dispersible tablets. The 2mg and 5mg dispersible tablets (mainly for paediatric use) were unaffected by the decision.

Parameters of the review:

The review is intended to be an "end to end" review of the systems and processes followed by PHARMAC in relation to the sole supply decision. In particular, it will address:

- all preliminary steps which led to the sole supply decision,
- all steps since taken to implement the decision,
- all steps responding to subsequent events.

For the avoidance of doubt, the review is not intended to be a reassessment of substantive decision making, but will include matters such as the sufficiency of the information provided to the decision maker.

The Independent Reviewer will have full access to PHARMAC's documentation and staff as required, subject only to any reasonable restrictions for legal, commercial, or privacy reasons.

The Reviewer will engage a suitably qualified clinical advisor (to be agreed between the Reviewer and PHARMAC) to provide independent guidance and advice to the Reviewer.

The Independent Reviewer is asked to provide findings in relation to the following matters:

- Was the decision-making process, including preliminary steps, followed by PHARMAC in relation to the lamotrigine sole supply decision appropriate?

- Was the design and execution of PHARMAC's implementation process for the lamotrigine sole supply decision appropriate?

- Given PHARMAC's role in the health sector, are there areas in which PHARMAC could improve its decision making and implementation processes for future brand changes, and if so what are these?

The following matters are out of scope of this review:

- The specifics of any matter currently before the Coroner

- Conduct by parties outside PHARMAC

- Findings regarding adverse events experienced by individual patients

- Matters of legal liability

- Matters relating to individual staff conduct or performance

- Matters relating to PHARMAC's statutory objective and/or the scope of PHARMAC's current role.

Deliverables, timeframes, and reporting

The Independent Reviewer is to provide a draft report for PHARMAC comment prior to producing a final report. The intended timing for delivery of the final report is early April 2020.

Appendix 2 – Associate Professor Doogue's advice

A/Prof Matthew Doogue
Department of Medicine
University of Otago, Christchurch

Dr Jonathan Coates
Claro

19 April 2020

Re: Independent Review of PHARMAC's Lamotrigine Sole Supply Decision

I am a qualified medical practitioner with vocational registration in the specialties of Clinical Pharmacology and Endocrinology (NZMC Registration No. 22733). My qualifications include MBChB and FRACP. I am employed by the University of Otago – Christchurch as Associate Professor of Medicine and by the Canterbury District Health Board (CDHB) as a Senior Medical Officer in Clinical Pharmacology and General Medicine and as Clinical Director of the Department of Clinical Pharmacology.

Clinical Pharmacology is the scientific discipline that involves all aspects of the relationship between drugs and humans. The clinical speciality includes all aspects of quality use of medicines. My academic role includes teaching clinical pharmacology from undergraduate to specialists and my research interests include adverse drug reactions and clinical decision.

I have been asked to provide clinical advice for the Independent Review of PHARMAC's Lamotrigine Sole Supply Decision. More specifically, I was asked to explain, bioequivalence and interchangeability. I was further asked to comment on aspects of the decision to move to one brand and to comment on implementation planning and risk mitigation. I was further asked to comment on PHARMAC's response to Medsafe's submissions and on quality assurance. I was provided with copies of PHARMAC documents pertaining to the matter and I accessed published literature and reports relevant to the questions asked. I have not listed these. I have selectively cited a small number of key references that are important to the questions asked.

I have read the terms of reference for the independent review of PHARMAC's lamotrigine sole supply decision. I note the parameters of the review state:

> *The review is intended to be an "end to end" review of the systems and processes followed by PHARMAC in relation to the sole supply decision. In particular, it will address:*
>
> - *all preliminary steps which led to the sole supply decision,*
> - *all steps since taken to implement the decision,*
> - *all steps responding to subsequent events.*
>
> *For the avoidance of doubt, the review is not intended to be a reassessment of substantive decision making, but will include matters such as the sufficiency of the information provided to the decision maker.*

Background

The issues raised here are not new and have been extensively discussed and documented many times. However, the level of knowledge and understanding of the issues in the health professions and the public is variable. Differences in perceptions of the issues can lead to differences in views and actions.

Examples of the state of knowledge in New Zealand include a special edition of the Best Practice Journal (BPAC) on generic medicines in 2009.[40] This explains the concepts and issues to a general clinical audience and illustrates the level of knowledge expected of a prescriber. There was a report on brand switches in New Zealand provided by MedSafe to the Medicines Adverse Reaction Committee in 2018.[41] This provides in depth review of previous experience in New Zealand of controversial brand changes. The findings in this review are similar to those in other countries. This can be summarised as, problems relating to brand switching are seldom pharmacological.

There is a long history of concerns about brand changes and of actions to protect the market position of different brands of medicines. In this respect medicines are similar to other widely used products. The difference between medicines and other products is how tightly medicines are regulated.

For a context most people are familiar with using different brands of flour or different brands of petrol. Flour (food) and petrol (fuel) are less tightly regulated than medicines. Food must list its ingredients and be produced in a safe way, this is less strict than for fuel or medicines.[42] Fuel must demonstrate 'quality' of product, this aspect is similar to medicines.[43] 'Quality' in this case means the product reliably has a certain chemical composition. For medicines there is regulation of both quality of the product AND additionally of the amount (rate and extent) of the drug in the blood of people taking the medicine. This is the concept of bioequivalence.

For medicines different brands must both have same amount of the medicine AND be bioequivalent.

Bioequivalence

> *Bioequivalence: taking one brand of a medicine gives the same amount of drug in the body as taking another brand.*

Two brands of the SAME medicine are bioequivalent when the SAME dose gives the SAME concentration of medicine in people taking the medicine. Functionally, this means that if two brands are bioequivalent, then the same dose is expected to produce the same clinical effect regardless of which brand is used.

A new ('comparator') brand must demonstrate bioequivalence to the existing ('reference') brand. The reference brand is usually the 'originator' brand, which has had safety and efficacy demonstrated in clinical trials. This process is also regulated.

To establish bioequivalence both steps must be demonstrated.[44] Firstly, the comparator must be manufactured to Good Manufacturing Practice (GMP) standard and contain the same amount of the active ingredient. Secondly, a bioequivalence study is undertaken to demonstrate equivalent bioavailability to ensure the comparator has the same pharmacokinetics as the originator.

[40] BPJ SE Generics May 2009 Best Practice Journal https://bpac.org.nz/BPJ/2009/generics/contents.aspx
[41] Brand switches in New Zealand. Medicines Adverse Reactions Committee: 13 September 2018 https://www.medsafe.govt.nz/committees/marc/reports/175-Brand%20Switches%20in%20New%20Zealand.pdf
[42] https://gazette.govt.nz/notice/id/2015-gs1889
[43] http://www.legislation.govt.nz/regulation/public/2011/0352/latest/whole.html
[44] New Zealand Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods https://www.medsafe.govt.nz/regulatory/Guideline/code.asp

The requirements of the bioequivalence study are that both the maximum concentration achieved and the area under the concentration-time curve of the comparator have geometric mean values and 90% confidence intervals within 80-125% of the mean values of the originator. For narrow therapeutic index drugs (including lamotrigine), a tighter value of 90-111% is used.

This is measured by studying a group of people given a dose of the comparator brand one day and a dose of the reference brand on another day. The concentration of the active drug in their blood is measured several times after each dose. The concentration of the drug in the people is compared between the two brands.

Medsafe is responsible for establishing that approved generic medicines are bioequivalent to the originator. It is the responsibility of the pharmaceutical company wishing to market and distribute the comparator in New Zealand to provide the information to MedSafe in an application for approval. This includes evidence of GMP and the bioequivalence study, or studies. The processes for this are rigorous and New Zealand is very similar in to Australia and Europe and similar to USA and Japan.[44]

For clarity, Medsafe is not responsible for unapproved products.

In the case of lamotrigine, bioequivalence between Logem and Lamictal was established prior to Logem being distributed in New Zealand. After reports of issues after switching brands this was reaffirmed by MedSafe in a Prescriber Update.[45]

Because lamotrigine brand change has been previously associated with uncertainty, differences (or not) between brands of lamotrigine has been more thoroughly studied than for most medicines. In addition to bioequivalence studies there are randomised trials that have demonstrated equivalent effects of different brands of lamotrigine.[46,47]

PHARMAC could reasonably conclude that for patients who take their medicines correctly, switching between brands of lamotrigine would not cause meaningful differences in drug exposure. PHARMAC could reasonably conclude the pharmacological effects of the brands would be the same.

> NB: within a brand no two tablets are exactly the same. There can be small differences within batches and between batches. Additionally there can be small changes over time (this is another concept ‘stability’). These are also regulated by Medsafe.

Interchangeability and Substitution

Interchangeability means that two brands are expected to produce the same results when consistently used. Substitutability means that they can be switched. To be substitutable they also have to be available in the same form (e.g. tablet or liquid) and packaging (e.g. blister pack or bottle). These terms are not always used consistently but further discussion is not needed for the purpose of this report. In New Zealand interchangeability of medicines is regulated by MedSafe.[48] MedSafe may gazette a brand as not interchangeable. The regulatory process is such that brand interchangeability is ‘expected’.

[45] Some medicines need to be prescribed by brand. Prescriber Update 40(4): 68–69, 2019 https://www.medsafe.govt.nz/profs/PUArticles/December2019/Some-medicines-need-to-be-prescribed-by-brand.htm
[46] Generic Lamotrigine Versus Brand-Name Lamictal Bioequivalence in Patients With Epilepsy: A Field Test of the FDA Bioequivalence Standard Epilepsia. 2015 Sep;56(9):1415-24. https://pubmed.ncbi.nlm.nih.gov/26201987/
[47] Bioequivalence Between Generic and Branded Lamotrigine in People With Epilepsy: The EQUIGEN Randomized Clinical Trial JAMA Neurol. 2017 Aug 1;74(8):919-926. https://pubmed.ncbi.nlm.nih.gov/28654954/
[48] New Zealand Regulatory Guidelines for Medicines (Volume 1, Edition 6.16, September 2014) https://www.medsafe.govt.nz/regulatory/Guideline/Full%20-%20NZ%20Regulatory%20Guidelines%20for%20Medicines.pdf

Interchangeability is necessary as supply of an individual brand cannot be guaranteed for ever and there are many circumstances when brands may need to be switched. In New Zealand we have very few different brands of medicines because we have a single purchaser, PHARMAC, negotiating with suppliers. In most countries, including Australia, there are usually many brands of a medicine available and substitution of brands is common.

This is particularly visible to consumers for medicines available for general sale or over the counter at pharmacies. On the supermarket shelf you can see two different brands of paracetamol side by side. There are more brands of these available in New Zealand because general sale items are not funded by the taxpayer and hence are purchased by retailers, rather than by PHARMAC.

Interchangeability is determined by the regulator and substitution is undertaken by the pharmacist at dispensing. This is defined in the medicines regulations.[49] In New Zealand when PHARMAC changes funded brands this affects a lot of people at the same time. In Australia each individual pharmacy negotiates with suppliers and changes usually affect a small number of people at a time. Prior to the awarding of sole supply to the Logem brand of lamotrigine there were three brands of lamotrigine available and substitution could occur. For example if a patient went to a different pharmacy they may not have stock of a particular brand. Pharmacists endeavour to maintain brand consistency for patients, particularly for narrow therapeutic index drugs, and make efforts to counsel patients when changes occur. However because there are many different medicines in use and supply changes, brand changes are common.

Interchangeability and substitution poses four potential risks:

- Confusion due to changes in packaging or tablet appearance etc. This can be compounded if a brand change has different strengths available e.g. brand A has 50mg capsules, but brand B only has 25mg capsules and therefore patients need to take two capsules of brand B. Note that Logem and Lamictal have the same strengths and so this is not a relevant factor for lamotrigine.
- Patients have pre-existing preferences for brands which can affect confidence, adherence to regimens and placebo/nocebo effects.
- Bioequivalence is usually established in healthy, young participants. There are physiological changes with age, disease and medicines which alter bioavailability (for example, gastric pH changes with age, disease (e.g. Zollinger-Ellison syndrome) and with medicines (e.g. omeprazole)). Theoretically, some formulations may be more resistant to these changes than others. However this has not been shown in practice. For lamotrigine the randomised controlled trials of brands did not find evidence of this in patients with epilepsy.[46,47]
- Bioequivalence is established with population pharmacokinetics. Theoretically, an individual may exhibit a difference masked by the population mean. This has not been shown in practice. An example where I might be concerned would be a patient who had short gut (from extensive bowel surgery) AND it was two different brands of modified release preparations.

The first two risks can be mitigated, but not eliminated, by patient counselling at the time of brand switching. All approved products in New Zealand must follow GMP which mitigates the risk of variability in product quality.

If there are still concerns in particular situations, lamotrigine drug concentrations can be measured in individual patients before and after significant changes in treatment. If unexpected clinical events occur drug concentrations are one of the tests used to investigate the reasons for changes.

[49] http://www.legislation.govt.nz/regulation/public/1984/0143/latest/whole.html

NB. For stable patients, the reference concentration would be the drug concentration in that patient prior to switching, rather than the reported population reference range.

Decision to move to one brand

The decision was based on advice of the PHARMAC Neurological Subcommittee.[50] The subcommittee concluded:

> ***"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"*

In my view these conclusions are consistent with and supported by the evidence as cited in this report. As referred to there are 'social risks' of brand change.

- The first of these is change in adherence, confusion and consequently not taking the medicine in the same way causing a difference in drug effects.
- A second risk is a change in placebo/nocebo effect – some of the effects of medicines are due non pharmacological factors which are affected by expectations and beliefs.
- A third risk is that events are occurring regardless and that any event occurring soon after a change may be attributed to the change. Association versus causation.

Patients with epilepsy report issues with brand changes more than some other conditions. The reasons for this are not well understood. A characteristic of epilepsy is that seizures are dramatic intermittent events that fluctuate in frequency. Changes to disease control in individuals happen and are not always easy to explain.

I have been asked specific questions related to this issue.

- Please explain the difference between the pharmacological risks and the other management (or 'social') risks associated with the move to the one brand (Logem).
    - See above

[50] PHARMAC. Record of the joint Neurological and Mental Health Subcommittee meeting held on 7 February 2019. 2019. Available from: http://www.pharmac.govt.nz/about/advice/ptac-subcommittees/

- Do you consider that there were material pharmacological risks (not management/social risks) with this brand change?
    - No, see above
- Do you think that PHARMAC, working through its subcommittees, had sufficient evidence to conclude that moving to one brand of lamotrigine was appropriate? (see, for example, the conclusion in the Neurological Subcommittee meeting minutes 11 November 2015 at 7.22).
    - Yes, as documented in the minutes of the Subcommittee
- Do you see significance in the Neurological Subcommittee's inability to reach a consensus as to whether lamotrigine should be in category one, two or three of the UK MHRA categorisation? (see 11 November 2015 minutes at 7,10, 7.12, and 7.21).
    - No. The UK MHRA categorisation has been useful. It is not an international regulatory standard, it is rather a categorisation to 'help' with decisions. The need for this categorisation has largely been superseded by regulators adopting tighter criteria for narrow therapeutic index drugs. This is illustrated by the more recent American Epilepsy Society position statement, discussed further under implementation.[51]
- Do you think PHARMAC's original exceptional circumstances criteria was adequate protection for the particular consumer group?
    - Yes.
- Insofar as the management/social issues of moving to Logem (as a sole brand) are concerned, how do the foreseeable consequences compare with brand changes in other areas?
    - Epilepsy is a particularly difficult condition for brand changes and it is foreseeable that any brand change in epilepsy treatment will be difficult. Another example where difficulties are foreseeable is transplant medicine.
    - This is reflected in the additional measures PHARMAC took and also demonstrated by the subsequent problems leading to this review.
    - The review by MedSafe of brand changes in New Zealand, cited above, addresses this issue in detail.[41] I have attached it as a supplement to this report because it addresses this, and related issues, in detail.

Implementation planning and risk mitigation

Firstly my response to the specific questions asked.

- Is it correct to say that implementation planning, and risk mitigation strategies, is directed at the management/social risks associated with the brand change to Logem?
    - Yes

[51] AES Position Statement on Generic Substitution of Antiepileptic Drugs. Epilepsy Curr. 2016 May-Jun;16(3):209-11. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4913860/

- Are there national or international standards and/or guidelines addressing brand changes of medications? Are there any that specifically address brand changes of anti-epileptic drugs (AEDs)?
    - Brand changes are a normal rather than an unusual occurrence, as outlined above. Brand changes are largely managed by pharmacists as outlined in the medicines regulations. Other health professionals, including prescribers have a responsibility to understand the issues of brand changes and support patients. There is guidance for health professionals about managing brand changes, for example the BPAC publication cited above.[40] BPAC was also one of the avenues used to communicate the change.[52]
    - In 2014 the MHRA (UK) issued guidance for the UK re anti-epileptic drugs, which was considered by and referred to by the Neurological subcommittee of PHARMAC. Although often cited, this guidance has been superseded. NB: Even if considered applicable this guidance would not alter the findings of this review.
    - In 2016, following the randomised clinical trials of lamotrigine brands, the American Epilepsy Society issued an updated position statement on generic antiepileptic drugs.51 with the following:
        1. *"The AES supports ongoing research by the FDA to study factors (e.g., extended-release products, tablet or capsule color and shape, nocebo effect) related to the generic substitution of AEDs in adults and children.*
        2. *The AES acknowledges that drug formulation substitution with FDA-approved generic products reduces cost without compromising efficacy.*
        3. *When dispensing medications to patients, healthcare professionals should ensure that a bioequivalent FDA-approved generic product is substituted for the brand or another generic AED. For example, an immediate-release generic product should not be dispensed as a substitute for a delayed-release or an extended-release product.*
        4. *Based on data showing that tablet or capsule color or shape and that statements about drug products impact patient adherence and drug response, healthcare professionals should exercise the highest standards of care when substituting generic products (4, 5).*
            a. *Patients or caregivers should be informed when substitution of a drug product results in a change in color or shape. Drug products that differ in color or shape should not be mixed in the same prescription vial to avoid confusion by the patient or caregiver.*
            b. *Descriptions of generic products for patients and caregivers should indicate that generic products are equivalent to the brand product. Patient counselling should not include descriptions of generic products as being a cheaper or lower-quality version of the brand product."*

- Have you identified any mitigation actions that you would expect to be taken that PHARMAC omitted to take?
    - The guidance offered by PHARMAC around switching was sufficient to inform good medicines counselling by doctors, pharmacists and nurses. Therapeutic drug monitoring was

[52] https://bpac.org.nz/2019/lamotrigine.aspx

suggested as a measure to help if needed. This is an effective measure to manage individuals (as discussed above) and can be used, but is not required, at brand change.

- Of note the brand was in existing use in New Zealand, this was not switching all patients from one brand to another but consolidation to use of a single brand.

Secondly I quote the MedSafe report to the Medicines Adverse Reaction Committee in 2018 cited above.[41]

> ***"6.0 DISCUSSION AND CONCLUSIONS***
>
> *Brand switches will continue to happen in New Zealand due to the function of Pharmac and the increasing number of generics on the market. Pharmac aligns with international consensus in the economic benefit of generic medicines, however it is apparent from reporting trends that there is a risk of adverse drug reactions when brand switches occur. Currently, Medsafe acts in a retroactive manner to brand switches, where increased reporting encourages reviews of the medicine, media statements and public assurance of safety and quality. Thus, there lies an opportunity to take on a more proactive approach, using general and targeted risk minimisation interventions to enhance public safety, reduce the potential for harm and improve public trust in Pharmac, Medsafe, and the wider government.*
>
> *On a New Zealand population-level, there is no evidence of issues with brand-switches (35). This is in line with international evidence on the effectiveness and economic benefits of generic medicines. The ADRs that are reported appear to be on an individual level and the causative mechanisms of such ADRs can be difficult to pin point. In the eye of public safety, exploring ways in which Medsafe can approach brand switches to reduce adverse reactions has become important, especially in light of the recent issues with Enlafax (venlafaxine).*
>
> *The ADRs that occur are likely not of any physiological mechanism, or due to pharmacological properties of the medicine. Theories as to how these come to be may be through negative perceptions and the nocebo effect – where the simple knowledge that the brand has changed may lead to adverse effects. An alternate explanation is that disease-related or non-related symptoms are being attributed to adverse effects associated with the brand switch – these are not true ADRs but are reported and treated as being ADRs. There are rare situations where a patient may have an intolerance to a changed excipient, however these would not be expected to occur at the observed rates.*
>
> *The media has been shown to play an increasingly important role in the reporting trends. In the early 2000s, brand switches generated ADR reports, but at a much lower number in comparison to recent switches. News was less accessible than it currently is, with online media, social media and discussion boards. Since the Eltroxin formulation issues, the media has started publishing more articles highlighting cases where patients state the cause of their adverse reactions are the brand switch. The validity of these articles are irrelevant to the core issue – media portrayal plays an important role in shaping the public's perception of the world and will directly stimulate certain trends. High reporting of venlafaxine ADRs directly following media reports is an excellent example of this effect. If only negative effects are [widely] publicised, there is a higher risk of the nocebo effect or misattribution of symptoms."*

The events that have played out with lamotrigine are similar to those on previous occasions and it is possible that media reports contributed to the confusion.

In my opinion PHARMAC's implementation planning and risk mitigation was of a high standard. Putting additional resources to this would have added cost and been unlikely to reduce risk.

Response to potential adverse reaction notifications

Management of the brand change and supporting patients is the responsibility of clinicians. This includes appropriate management of any reported changes by the patient.

I was asked

- Should any quality control/assurance have been undertaken in 2019, following the adverse reaction notifications, to test the Logem? If so, whose job would this have been?
    - The primary responsibility to report potential adverse events sits with health professionals. Reporting is to CARM (Centre for Adverse Drug Reactions Monitoring). If there are specific concerns then a heath professional should undertake further investigations and/or refer onwards.
    - If there were thought to be issues of product quality, then this would have implications for approval. The manufacturer has responsibility for product quality and Medsafe has regulatory responsibility. Any concerns about product quality should be raised with Medsafe.
    - I have not reviewed the clinical events to be able to comment further. To do so I would need access to other sources of information and an extension of the scope of the review.

Following reports of problems, the media reports and the reported statements of some health professionals may have further contributed to the problem. The possibility of problems was foreseen and the reasons for such problems are known. Attributing the cause of the problems to the pharmacological effects of the Logem brand risks diagnostic error and consequent management errors. This possibility cannot be excluded and needs to be investigated but apriori causality is unlikely.

Following the concerns that were raised, PHARMAC widened criteria for funded access to other brands and provided funding for patient appointment with GPs. The application criteria for other brands are:

- Break through seizures
- Mood destabilisation
- Concerns regarding driving
- Clinical concerns around the patient's ability to manage a brand change (e.g. previous difficulty with medicine changes, severe anxiety around change

These are broad criteria. While an understandable response to public concern such broad criteria may not be appropriate in future similar circumstances. I would suggest that in future similar circumstances funding an alternative brand may not be an appropriate response.

To illustrate this, consider a patient with another condition treated with a particular brand of a medicine who develops problems. A brand change is not expected to help and would not be an appropriate clinical course of action. A temporal association with brand change understandably raises questions, but accumulated evidence suggests brand change per se is unlikely to cause a biochemical change.

In responding, PHARMACs has broad objectives outlined in the PHARMAC framework including 'need' and 'health benefit'. These include social impacts and managing additional risks such as patients stopping their medicines. The responsibility for individual patients sits with their clinicians.

General comments

For lamotrigine, information that no pharmacological consequences were likely was available prior to the brand change. The evidence for this was stronger than for almost any other brand change.

This does not exclude problems occurring. I have not considered what problems occurred and why and detailed examination of each case is required before conclusions can be drawn. This should include careful analysis of clinical events and measurement of drug concentrations. This is outside the scope of this review.

Brand switching of medicines is emotive for patients and health professionals. Epilepsy is particularly challenging as it is a fluctuating condition with dramatic intermittent events. It is understandable and expected that seizures and other events associated with a brand change may be attributed to the brand change. However, to determine causality requires detailed investigation. In previous brand changes subsequent investigation has found that associated events were not caused by the brand changes.

The role and responsibilities of the clinicians and media is not in scope of this review. However, based on previous problems with brand changes, the solutions to avoiding future problems are likely to be with clinicians, media and patient groups, rather than with bodies such as PHARMAC. If there is to be further external scrutiny, this should be considered.

Appendix 3 – PHARMAC representatives interviewed

The following PHARMAC representatives were interviewed as part of this review (either in person or by telephone)

Sarah Fitt, Chief Executive

Lisa Williams, Director of Operations

Adrienne Martin, Senior Therapeutic Group Manager

Adam McRae, Senior Implementation Lead

Dr Ken Clark, Acting Medical Director

Dr Peter Murray, Deputy Medical Director

David Lui, Chair, Consumer Advisory Committee

Professor Mark Weatherall, Chair, Pharmacological and Therapeutics Advisory Committee