THIS FINDING IS SUBJECT TO PROHIBITIONS AND RESTRICTIONS ON PUBLICATION UNDER S74 OF THE CORONERS ACT 2006

IN THE CORONERS COURT AT AUCKLAND

CSU-2019-CCH-000721
CSU-2019-DUN-000322
CSU-2020-ROT-000070
CSU-2019-AUK-001526
CSU-2019-DUN-000248
CSU-2019-HAS-000223

UNDER **THE CORONERS ACT 2006**

AND

IN THE MATTER OF **An inquiry into the deaths of**
Ricky Adam Wayne BLACKLER
Reuben Campbell BROWN
Krystle Michelle LOYE
Andre MADDOCK
William Colin OLIVER
Jessica Louise REID

Date of Hearing: 30 November – 2 December 2020
22 February – 4 March 2021

Appearances: Gary Blackler, Dellys Brown, Gary Loye, Nadia Jooste, Johanna Oliver, Hannah Reid (Families' Representatives)

Dr Robert Sweeney, Dr Yun Yang, Matthew McClelland QC for Dr David Sharples, Dr Luke Ivancevic, Dr Joshua Tang, Dr Conor Cosgrave; Maree Cowan for Dr Cosgrave

Dr Kate White; Dr John Mottershead; Jane Hanna; Lisa Williams; Professor Mark Weatherall; Associate Professor Natalie Medlicott; Dr Elizabeth Walker

Mike Colson and Laura Hardcastle (for Pharmac)

Adam Holloway (for Dr Sharpe)

Chris James (Medsafe)

Sarah Wroe, Iswari Jayanandan and Maree Cross (for Loye, Maddock & Oliver)

Heather Ruddell (Police)

Bridget Sinclair (for pharmacists)

Todd Simmonds and Silva Hinek (counsel to assist the Coroner)

Date of Findings: 17 May 2021

FINDINGS OF JUDGE D MARSHALL

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Introduction

[1] Epilepsy is a common neurological disorder affecting one to two percent of the population in New Zealand. Epilepsy is defined as a tendency to have recurrent seizures. The seizures are caused by uncontrolled electrical activity in the brain. Approximately 70% of people with epilepsy will be able to control it well with medication.

[2] Antiepileptic drugs (AEDs) are used to treat epilepsy. AEDs work by changing the levels of chemicals in the brain. They can stop seizures happening.

[3] A company that creates a new medicine is called the innovator. An innovator would usually take out a patent on a new drug. The innovator will have borne the costs of developing the innovator drug. Once the patent has expired, other companies can produce generic brands of the innovator brand drug. The generic brands will have the same active ingredient as the innovator, at the same strengths. They may be able to be supplied at a lesser cost than the innovator brand.

[4] Medicine suppliers have the rights to market and supply a particular medicine and may be the manufacturer of the medicine or an intermediary.[1]

[5] Lamotrigine is a form of AED. Lamictal is the innovator brand. Arrow-Lamotrigine and Logem are generic brands of lamotrigine.

[6] Medsafe is the New Zealand Medicines and Medical Devices Safety Authority. It is a business unit of the Ministry of Health. Its stated goal is "To enhance the health of New Zealanders by regulating medicines and medical devices to maximise safety and benefit."[2]

[7] The Centre for Adverse Reactions Monitoring (CARM), is contracted by Medsafe to collect and analyse adverse reaction reports for any medicine. Adverse reaction

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[1] All Parties Bundle (APB), p 1479 (Lisa Williams Brief, 5 February 2021, para 2.1).
[2] www.medsafe.govt.nz.

reports come from many sources, including healthcare professionals, consumers and companies.[3]

[8] Pharmac is a Crown entity responsible for deciding which medicines and medical devices are publicly funded in New Zealand. Its stated objectives include securing the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of available funding.[4]

[9] If a company wishes to sell a medicine in New Zealand they must make an application to Medsafe. The company concerned must provide information to Medsafe, including information about the active ingredient of the medication and the non-active ingredients (excipients) present in the medicine.

[10] For generic medicines, the manufacturing company conducts bioequivalence studies. Bioequivalence does not mean that the medicine is therapeutically equivalent to the innovator medicine. Evidence given during the inquest from Professor Weatherall was that the terms "bioequivalence" and "therapeutic equivalence" refer to different things. Bioequivalence refers to whether two medicines result in equivalent concentrations of the active ingredient in the blood. Therapeutic equivalence refers to whether two medicines have the same therapeutic effect. Professor Weatherall's evidence was that it is generally assumed that medicines which exist in equivalent concentrations in the blood will have equivalent therapeutic effects, since it is the plasma concentration which determines the effect of the medicine. As far as he is aware, no competent regulator in the world requires therapeutic equivalence studies for medicines such as lamotrigine.[5]

[11] In the case of Logem, the bioequivalence study (the Study) was designed by Mylan (the Logem manufacturer) to assist in establishing the bioequivalence of Logem and Lamictal in accordance with the European Medicines Agency's *Guideline on the Investigation of Bioequivalence*. The study was conducted in 2003 and

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[3] Notes of Evidence (NOE) Part 2, pp 46-47.
[4] New Zealand Public Health and Disability Act 2000, s 47 (a).
[5] APB, pp 1776-1777 (Mark Weatherall Supplementary Brief, 19 March 2021, paras 2.3-2.4).

involved 24 healthy subjects being given a single dose of Lamictal and a single dose of Logem, and their plasma levels measured after each dose.

[12] According to Medsafe, by demonstrating bioequivalence, the Study shows that a new patient starting on a lamotrigine containing medicine should expect the same safety and efficacy profile whether taking Logem or Lamictal. The Study was not designed to show:

(a) Whether a patient already stable on a particular brand can safely switch to taking a different brand.

(b) "therapeutic equivalence" between the two brands for individual patients.[6]

[13] There is no requirement in New Zealand or internationally for either of those aspects to be demonstrated prior to granting regulatory approval for a new generic medicine.

[14] Medsafe advises that:

> The active ingredient in a generic medicine is the same as that contained in the respective innovator (brand name) medicine. Therefore, if the amount of active ingredient released into the blood is the same for both products then the effect is the same. Bioequivalence studies are performed to show that in healthy volunteers the level of active ingredients is the same whether an innovator or generic product is taken.[7]

[15] The Group Manager for Medsafe, Chris James, gave evidence that Medsafe has expert assessors who look at bioequivalence studies supplied by manufacturers to ensure the studies are designed and conducted in line with internationally accepted guidelines.[8]

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[6] APB, p 1723 (Letter from Medsafe (Chris James), 17 March 2021).
[7] APB, p 299 (Letter from Medsafe (Chris James), 17 February 2020).
[8] NOE Part 2, p 40.

[16] Medsafe first approved the Lamictal brand of lamotrigine in December 1992 and it was funded by Pharmac in 1994. Lamictal was the innovator product. A generic brand, Arrow-Lamotrigine, was approved by Medsafe in July 2006. [9]

[17] In September 2006 Logem was approved as a generic of Lamictal. Medsafe considered, amongst other things, the Study comparing the bioequivalence of Logem to Lamictal.

[18] Mr James' evidence was that other countries have approved Logem as a generic brand including Australia, Canada, Germany, United Kingdom, Spain, France and the Netherlands.

[19] A record of 2018 pharmaceutical claims show that 50% of approximately 12,500 patients in New Zealand collecting a funded lamotrigine prescription that year had changed brands at least once since they first commenced treatment with lamotrigine while around 4,000 had changed two or more times (including 365 patients who changed brands at least 10 times).[10]

[20] The following explanation is taken from a report commissioned by Pharmac:

> 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 leads 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 this decision-making, Pharmac has established a framework *The Factors for Consideration*. The four main factors for consideration are:
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> > 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.

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[9] APB, p 1485 (Lisa Williams Brief, 5 February 2021, para 3.4).
[10] APB, p 172 (Pharmac memorandum for board meeting 29 March 2019).

> Suitability – the nonclinical features of the medicine that might impact on health outcomes.[11]

[21] On 29 March 2019, Pharmac's Board decided to award the sole supply of the drug lamotrigine to a single brand, Logem.

[22] Pharmac implemented a five-month transition period, starting on 1 May 2019, during which three brands of lamotrigine were funded while steps were taken to introduce Logem as the only funded brand. Logem became the only funded brand on 1 October 2019.

[23] Following the introduction of Logem as the only funded brand, there was increased media and public interest in the brand switch. CARM received reports of adverse reactions of patients who switched to Logem.

[24] Several deaths were reported of individuals who suffered from epilepsy and who died suddenly. Given the media and public interest in this issue I decided to hold a joint inquest into six deaths of patients with epilepsy pursuant to section 84 of the Coroners Act 2006.

[25] Part 1 of the inquest was held at the Auckland District Court during the week beginning 30 November 2020.

[26] Part 2 was held during the week beginning 22 February 2021 and concluded on 4 March 2021.

Issues for the Inquest

[27] Two pre-inquest teleconferences were held before the inquest started. It was agreed that the following issues were relevant to my inquiry.

(a) What was the cause of death for each of the deceased?

(b) What were the circumstances of each death?

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[11] APB, p 468 (Independent Review of Pharmac's Lamotrigine Sole Supply Decision, Dr Jonathan Coates, 12 May 2020, para 4.3).

(c) Had the deceased switched to Logem?

(d) If so, did the deceased or their next of kin know about the switch?

(e) If so, how did they know about it - who told them, what were they told and were they given advice about what to do in case of adverse reactions/symptoms?

(f) Were any changes or adverse reactions noted after the switch and if so, were the deceased or their next of kin aware of the need to seek medical advice? Did they know about the option to request exceptional circumstances funding?

(g) Did any of the deceased express anxiety about the switch and if so, what, if anything, was done?

(h) What steps did Pharmac take to implement the brand switch and in particular:

(i) What advice was given to prescribers (general practitioners, nurse practitioners and specialists)?

(ii) How was the brand switch fee implemented?

(iii) What advice was given to pharmacists?

(iv) How was the switch communicated to interest groups, such as Epilepsy New Zealand?

(v) How was the switch communicated to consumers?

(vi) Was any monitoring put in place by Pharmac to ensure that consumers were given appropriate information about the switch?

(i) Was Logem bioequivalent to the brands it replaced?

(j) Apart from reports to CARM, is there any other national system of monitoring generic medications to determine therapeutic equivalency and if not, should there be?

Background to the Brand Switch

[28] Under s 49 of the New Zealand Public Health and Disability Act 2000 (NZPHDA) Pharmac is obliged to 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 must take measures to inform the public, groups, and individuals of Pharmac's decisions concerning the pharmaceutical schedule.

[29] Pharmac has two advisory committees, the Pharmacological and Therapeutics Advisory Committee ("PTAC") and a Consumer Advisory Committee ("CAC"). PTAC's role is to provide objective advice to Pharmac on pharmaceuticals and their benefits.[12] The CAC's role is to provide input from a consumer or patient point of view.[13]

[30] PTAC has several subcommittees, including the Neurological Subcommittee and a Mental Health Subcommittee. These subcommittees met on multiple occasions in relation to AEDs and brand switches.

2007 Neurological Subcommittee Meeting

[31] On 19 April 2007, the Neurological Subcommittee undertook a therapeutic group review of AEDs. The Subcommittee considered that "patients stabilised on one brand of lamotrigine should not switch brands PTAC accepted the recommendation.

2009 Neurological Subcommittee meeting

[32] In April 2009, the Neurological Subcommittee met and discussed another AED, sodium valproate. The committee noted that patients cannot drive for up to 12 months following a seizure and 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."[14]

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[12] NZPHDA, s 50(1)(a).
[13] NZHPDA, s 50(1)(b).
[14] APB, p 471 (Independent Review of Pharmac's Lamotrigine Sole Supply Decision, Dr Jonathan Coates, 12 May 2020, para 5.7).

2010 Neurological Subcommittee meeting

[33] There was further discussion of another AED at this meeting and concern was expressed at the high expenditure on that brand. The Subcommittee, "…reiterated its previous comments that it would be supportive of an arrangement where a (cheaper) generic brand would be the only funded brand 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.[15]

2012 Neurological Subcommittee meeting

[34] At this meeting the Neurological Subcommittee noted that there were "potentially greater risks associated with switching between generic products compared with switching between the innovator brand and a generic brand."[16]

2013 PTAC meeting

[35] At this meeting PTAC concluded that, at that time, mandatory switching of AEDs would not be appropriate.[17]

2015 Neurological Subcommittee meeting

[36] At this meeting the Neurological Subcommittee considered published literature and concluded, "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."[18]

[37] The Subcommittee concluded in part that:

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[15] APB, p 472 (Independent Review of Pharmac's Lamotrigine Sole Supply Decision, Dr Jonathan Coates, 12 May 2020, para 5.10).
[16] APB, p 472 (Independent Review of Pharmac's Lamotrigine Sole Supply Decision, Dr Jonathan Coates, 12 May 2020, para 5.14).
[17] APB, p 1621 (Record of the PTAC meeting, 1 & 2 August 2013, para 6.29).
[18] APB, p 9 (Record of the Neurological Subcommittee of PTAC meeting, 11 November 2015, para 3.7).

(a) A managed brand switch to one brand of lamotrigine would be preferable to having multiple brands listed (as was the case in 2015).

(b) A competitive process for a sole supply agreement would be appropriate if there was a suitable transition period.

(c) A three to six-month transition period would be needed.

(d) Patients who were unable to transition could be considered for Exceptional Circumstances funding.

(e) There were no blood tests that would assist with monitoring the impacts of the brand change.

(f) Patients are generally averse to change and if there was a brand switch any change in seizure frequency could be perceived to have been caused by a change in brand.

(g) Health professionals would be important to provide support and reassurance around brand changes.

(h) The most important factor for maintaining epilepsy control was medication adherence.

(i) General Practitioners (GPs) and pharmacists would be the health professionals most likely to be involved in supporting a brand change if it occurred.

2016 Neurological and Mental Health Subcommittee meetings

[38] The Neurological Subcommittee considered Pharmac's proposal to tender for a sole supplier of lamotrigine and did not express any concerns.[19]

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[19] APB, p 14 (Record of the Neurological Subcommittee of PTAC meeting, 7 November 2016, para 1.1).

[39] Similarly, the Mental Health Subcommittee met on 23 November 2016 and concluded that there would be no problems clinically from a mental health standpoint, to brands of lamotrigine being changed and noted this already occurred at the pharmacy level.

[40] In the UK, the regulation of changes of medicines is covered by the Medicines and Healthcare Products Regulating Agency (MHRA) 2013 guidelines (and its 2017 update) on switching AEDs which are subject to consultation with patients. In the guideline, lamotrigine is a category 2 drug meaning that the advice to health professionals is to base the need for continued supply of a particular manufacturer's product on clinical judgement and consultation with the patient and/or carer, taking into account factors such as seizure frequency and treatment history. It is also to take account of patient, carer related factors such as negative perceptions about alternative products and/or issues related to the patient. The patient related factors should be considered when deciding whether it is necessary to maintain supply continuity for a specific product and that reports of loss of seizure control and/or worsening side-effects should not be ruled out in all cases as chance associations. [20]

[41] Professor Weatherall, the chair of PTAC, gave evidence that the Neurological Subcommittee members were unable to reach a consensus on the appropriate classification of lamotrigine under the MHRA guidelines but did agree that a managed change to a single brand of lamotrigine would be preferable to having multiple brands listed (and therefore patients potentially being changed at the pharmacy level). In Professor Weatherall's view this was equivalent to their preferred approach for category 2 medicines under the MHRA guidelines, that there should be a managed brand switch.[21] The Subcommittee also accepted that epilepsy control would be monitored by assessing seizure frequency.[22] They also considered that it was unnecessary for every single patient to be individually counselled by the prescriber regarding the brand switch and that pharmacists would be central to the brand switch and if there were concerns, the patient could then see their GP.[23]

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[20] APB, p 318 (Letter from Medsafe to Pharmac, 19 September 2018).
[21] APB, p 10 (Record of the Neurological Subcommittee of PTAC meeting, 11 November 2015, para 3.14). See also APB, p 1547 (Mark Weatherall Brief, 15 February 2021, para 2.4).
[22] APB, p 1547 (Mark Weatherall Brief, 15 February 2021, para 2.6).
[23] APB, p 1551 (Mark Weatherall Brief, 15 February 2021, para 2.18); NOE Part 2, p 159.

[42] The Subcommittee also considered there were no blood tests which might be used to monitor changes since serum level monitoring was only useful for medicines with a narrow therapeutic index which lamotrigine was not.[24]

Implementation

[43] On 18 June 2018, Pharmac issued a Request for Proposal ("RFP") for the supply of lamotrigine. The RFP Evaluation Committee selected the proposal submitted by Mylan (Logem brand).[25]

[44] Pharmac released a consultation document on 28 August 2018, with consultation closing on 26 September 2018. The consultation documents were published on the Pharmac website with hyperlinks to the various Subcommittee minutes. The consultation documents were also emailed to subscribers on Pharmac's neurology and mental health distribution lists and were offered to "Key stakeholders" including

(a) Epilepsy New Zealand

(b) The Epilepsy Foundation

(c) The New Zealand League against Epilepsy

(d) Epilepsy nurse specialists known to Pharmac

(e) New Zealand Transport Agency

(f) Organisations representing GP's, including General Practice New Zealand, the New Zealand Medical Association and the Royal New Zealand College of General Practitioners

(g) Organisations representing pharmacists, including the Pharmaceutical Society of New Zealand and the Pharmacy Guild and

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[24] APB, p 1547 (Mark Weatherall Brief, 15 February 2021, para 2.6).
[25] APB, p 1489 (Lisa Williams Brief, 5 February 2021, para 3.12).

(h) Other key stakeholders including the Mental Health Foundation. [26]

[45] Pharmac received submissions from 32 parties and decided to delay taking the proposal to Pharmac's Board.[27]

[46] Medsafe was one of the submitters. Medsafe opposed the switch but if the switch was to happen:

(a) Patients should be reviewed by the GP before changing brands and counselling should be provided by the GP. GPs should refer the most vulnerable patients (being those who are seizure-free and those with labile (unstable) seizures for specialist oversight.

(b) All patients should be actively followed up to check that they are coping with the change.[28]

[47] At the inquest, Mr James' evidence was that Medsafe were looking for a "long implementation period that would enable all patients to have that discussion with their prescriber to ensure that they were aware of a change, to consider what factors might need to be taken into account in terms of monitoring."[29]

[48] The joint Neurological and Mental Health Subcommittee's view was that Medsafe's definition of vulnerable patients was too broad and that referral of all such patients would place an unnecessary and significant burden on specialists. The joint Subcommittee also considered that clinical judgement regarding vulnerable patients should be exercised by the GP and that routine testing of lamotrigine levels in patients' plasma would be unnecessary as the majority of patients would be likely to remain adherent to the medication throughout the change.[30]

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[26] APB, p 1489 (Lisa Williams Brief, 5 February 2021, para 3.12).
[27] APB, p 1490 (Lisa Williams Brief, 5 February 2021, para 3.13).
[28] APB, pp100 – 101 (Neurological and Mental Health Subcommittee Memorandum, January 2019). See also APB, pp 317 (Letter from Medsafe to Pharmac, 19 September 2018) and p 322 (Letter from Medsafe to Pharmac, 21 November 2018).
[29] NOE Part 2, p 63.
[30] APB, pp 59, 61 (Record of the Joint Neurological and Mental Health Subcommittee Meeting, 7 February 2019, paras 1.24, 1.27).

[49] An internal Pharmac memorandum noted the following risks for the brand switch.

(a) 89% of patients (approximately 10,700 people) would be required to transition to Logem.

(b) There was a risk that if patients suffered adverse effects during the transition that they would be associated with the brand switch.[31]

[50] As a result, Pharmac developed various implementation activities including:

(a) Holding regular face-to-face meetings with CARM.

(b) Providing a brand switch form for pharmacists to claim reimbursement for the additional time they may have spent supporting their patients with the change.

(c) Providing a counselling fee for GPs who had to spend additional time supporting their patients.

(d) Relaunching the "Beyond the Brand" online learning module.

(e) Providing a training opportunity for Epilepsy Association field officers working in the community and attending meetings with Epilepsy New Zealand.

(f) Developing a patient specific information leaflet to be used by healthcare providers.

(g) Providing information on Pharmac's website for prescribers, pharmacists and consumers.

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[31] APB, p 477 (Independent review of Pharmac's Lamotrigine sole supply decision, Dr Jonathan Coates, 12 May 2020, para 5.44).

(h) Requesting Best Practice Advocacy Centre New Zealand[32] (BPAC) to provide a written resource for primary care providers. The article was sent to over 10,000 members on BPAC's mailing list and was on the BPAC website.[33]

[51] There was also an 0800 number for general enquiries, a general enquiries inbox and a social media platform to answer questions.

[52] Pharmac met with Medsafe on 13 November 2018 to discuss Medsafe's concerns. As a result of the discussions, Pharmac decided to seek further clinical advice from the Neurological and Mental Health Subcommittees.[34]

[53] On 7 February 2019, a joint meeting of the Neurological and Mental Health Subcommittee took place.[35] The members had considered the consultation feedback and other material, including publications reviewed by PTAC in November 2015, publications provided by Medsafe and publications provided during the consultation process. The members noted that:

> Some of the smaller case series reported that brand changes of lamotrigine were associated with loss of seizure control and adverse reactions … However, the majority of the evidence provided by studies of higher quality and less subject to bias, such as prospective and retrospective cohort studies, and systematic reviews of the broad range of evidence, reported that there was unlikely to be important clinical risks as a result of changing between brand and generic lamotrigine for the majority of patients.[36]

[54] They also noted that, due to the nature of epilepsy there is a risk of seizure recurrence among patients who have been seizure-free for a prolonged period, even whilst receiving a stable treatment regimen.[37]

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[32] An independent not for profit organisation that delivers educational continuing educational and continuing professional development to medical practitioners and other health professional groups. Bpac.org.nz.
[33] APB, pp 1495-1497, 1519-1520 (Lisa Williams Brief, paras 4.7-4.9, 5.69).
[34] APB, p 1491 (Lisa Williams Brief, 5 February 2021, para 3.15).
[35] APB, pp 51-64 (Record of the Joint Neurological and Mental Health Subcommittee Meeting, 7 February 2019).
[36] APB, p 54 (Record of the Joint Neurological and Mental Health Subcommittee Meeting, 7 February 2019, para 1.4).
[37] APB, p 57 (Record of the Joint Neurological and Mental Health Subcommittee Meeting, 7 February 2019, para 1.10).

[55] The Subcommittee concluded that:

> … based on the available evidence, there was no pharmacological reason to suggest there would be a clinical problem with changing brands of lamotrigine for patients with epilepsy or mental health conditions. The Subcommittee considered that patients experience adverse events (e.g. breakthrough seizures) even when there is no brand change. The Subcommittee considered that in the event of a brand change there would be patients who experience adverse events that would attribute these to the change, and that factors likely to contribute to this perception could include reduced adherence, nocebo[38], or other psychological factors.[39]

[56] The Subcommittee also noted that moving to sole supply of one brand of lamotrigine would reduce future inadvertent and uncontrolled brand changing from taking place. It considered the implementation activities proposed by Pharmac were appropriate. These included:

(a) Development of Pharmac resources specifically for prescribers, pharmacists and patients to support a change in brand.[40]

(b) Consideration to covering primary care appointment fees for those patients requiring specific support with the lamotrigine brand change.

(c) Pharmac website information, including a video providing lamotrigine brand change information.

(d) Supporting consumer facing organisations who work with people in the community changing their brand of lamotrigine.

(e) Regular meetings with CARM, Medsafe and Pharmac to ensure consistency of health sector approach.

(f) Development of a written resource for primary health care professionals, outlining how to support patients with a change and any impacts.

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[38] Nocebo is a negative expectation of treatment leading to a more negative effect.
[39] APB, p 58 (Record of the Joint Neurological and Mental Health Subcommittee Meeting, 7 February 2019, para 1.14).
[40] The pamphlet produced for patients did not refer to the GP co-payment, the alternative funding regime or any side effects that might occur to a minority of patients.

(g) Consideration of an alternative Pharmac funding mechanism for patients to remain on a particular brand of lamotrigine if unable to be transitioned to a new brand.[41]

[57] The Subcommittee considered that there was a risk of causing unnecessary anxiety about the change if too much emphasis was placed on it and that caution should be taken with the amount of information provided to patients up front. It thought a three to six-month transition period was reasonable.

[58] The proposal was taken to the Pharmac Board on 29 March 2019 and was approved.[42] Pharmac began its implementation processes.

[59] On 11 April 2019, Pharmac issued a notice of their decision to move to one funded brand of lamotrigine – Logem. The notice advised that from 1 October 2019 there would be only one funded brand and that reducing the number of brands of lamotrigine would free up more than $30 million over the next five years which Pharmac could use to fund other medicines for New Zealanders. There was to be a five-month transition period.[43]

[60] Pharmac accepted the advice that there was no pharmacological reason to suggest there would be clinical problems from changing brands of lamotrigine for the majority of patients with epilepsy or mental health conditions but also accepted there would be a minority for whom it may not be fine.[44]

[61] On 26 April 2019, Pharmac updated the Pharmaceutical Schedule to reflect the new arrangements. Updates are published monthly, with hard copies published three times yearly. On 26 April 2019, the hard copy of the Pharmaceutical Schedule update regarding lamotrigine was posted to approximately 1000 subscribers.[45]

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[41] APB, p 62 (Record of the Joint Neurological and Mental Health Subcommittee Meeting, 7 February 2019, para 1.32).
[42] APB, p 1491 (Lisa Williams Brief, 5 February 2021, paras 3.17, 3.18.
[43] APB, pp 65 – 71 (Pharmac notice, 11 April 2019).
[44] NOE Part 2, p 92.
[45] APB, pp 1512-1513 (Lisa Williams Brief, 5 February 2021, paras 5.40, 5.41).

[62] Notifications about the brand switch were sent to District Health Boards, Primary Health Organisations, pharmacy professional bodies, medical professional bodies, epilepsy nurse specialists that Pharmac were aware of and anyone who had opted into Pharmac's neurology and mental health mailing list.[46]

[63] In June 2019 Pharmac held an "ask me anything" event on Facebook.

[64] In August 2019, Pharmac developed a contingency plan for issues that might arise during the transition. This included identifying possible risk scenarios.[47] The contingency plan provided for the establishment of a dedicated Implementation Project Team. The team comprised members from Pharmac's medical directorate, the pharmaceutical funding team, implementation team and communications personnel who were to lead implementation activities.[48]

[65] The Implementation Team reviewed dispensing records to keep track of the number of patients who had changed funded brand and reviewed adverse reaction reports (from CARM and those reported to Pharmac). They also took into account the volume of exceptional circumstances applications received.[49]

[66] Applications for Pharmac Exceptional Circumstances funding is usually assessed through the Named Patient Pharmaceutical Assessment (NPPA) policy. Pharmac staff organised a meeting with members of the NPPA advisory panel as it was expected that the majority of applications in relation to Logem would be unlikely to meet all of the principles of the NPPA policy, so discretion would be needed when considering the applications. A specific form was developed in relation to the Logem brand and this was loaded onto the Pharmac website.[50]

[67] The transition period ended on 1 October 2019 and, after that date, the sole supply decision was implemented.

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[46] APB, pp 1507-1508 (Lisa Williams Brief, 5 February 2021, paras 5.24-5.26).
[47] APB, pp 84-93(Lamotrigine brand change contingency plan).
[48] APB, p 1499 (Lisa Williams Brief, 5 February 2021, para 4.17).
[49] APB, p 1523 (Lisa Williams Brief, 5 February 2021, paras 5.78-5.79).
[50] APB, pp 1504-1505 (Lisa Williams Brief, 5 February 2021, paras 5.15-5.17).

[68] On 12 November 2019, Medsafe issued a monitoring communication regarding adverse reaction reports, including (at that time) three deaths. This was followed by a period of negative media coverage and public concern.

[69] Given the level of public concern, Pharmac announced (on 15 November 2019) that there would be a revisiting of access to the Exceptional Circumstances Framework for lamotrigine. Pharmac did not want patients to stop taking the medication out of fear. The changes in the criteria were communicated through a media release on the Pharmac website, an update to all interested stakeholders, conversations with Epilepsy New Zealand, developing messaging and FAQs, writing to key professional bodies and requesting that BPAC provide a news update. As a result of this change, Pharmac received a large number of exceptional circumstances funding applications and advises that by 17 February 2020, approximately 2130 applications had been approved.[51]

[70] Pharmac advises that it received 99 applications for exceptional circumstances funding prior to 15 November 2019. One of these appeared to have been submitted due to a misunderstanding and was not pursued. Of the 98 applications that were assessed, 85 were approved and 13 were not approved prior to 15 November 2019. Of those 13, four were closed after requests for further information went unanswered and nine were declined.

[71] Reasons for making applications included:

(a) Side effects experienced and attributed to brand switch

(b) Breakthrough seizures

(c) Anxiety about the switch (risks of loss of driver licence, risk of side effects and risk of seizure).[52]

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[51] APB, pp 1525-1528 (Lisa Williams Brief, 5 February 2021, paras 6.3-6.9).
[52] APB, pp 1788-1792 (Lisa Williams Supplementary Brief, 19 March 2021).

Medsafe's View of the Brand Switch

[72] Medsafe's evidence[53] was that most generic medicines can be freely substituted but there are a small group of medicines where it is recommended to prescribe by brand and that AEDs are in that category.

[73] Medsafe agreed with the guidelines produced by the MHRA which, as noted earlier, places lamotrigine as a Category 2 drug.[54]

[74] Medsafe advises its concern:

> ...does not reflect a poor approval process or a flaw in the process for approving generic medicines. Instead it highlights the fact that there are a few patients who experience a clinically significant difference in the amount of active ingredient reaching the blood, as mentioned above. For antiepileptic medicines a change in the blood level of the active ingredient can result in significant adverse events for the patient.[55]

[75] In Medsafe's letter to Pharmac dated 19 September 2018, Medsafe warned that the brand switch proposal went against international consensus on switching between brands of antiepileptic medicines and it posed a potential significant safety issue.[56]

[76] In a letter of 21 November 2018, Medsafe recommended that if the brand switch was to go ahead, patients should be first reviewed by their GPs and the switch should not occur when the patient reaches the pharmacy without prior counselling by the GP. It also recommended that GPs refer the most vulnerable patients for specialist intervention to oversee and monitor the switch[57].

[77] Vulnerable patients were considered by Medsafe to be those who had been seizure-free. This was because the impact of a seizure could be profound. Those with labile seizures were also considered vulnerable as any variability could lead to loss of control. The letter also noted that patients with epilepsy may have memory problems or learning difficulties and therefore a patient leaflet would be needed. Medsafe went on to recommend that professionals and patients be reminded of the symptoms which

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[53] APB, p 300 (Letter from Medsafe (Chris James), 17 February 2020). .
[54] APB, p 316 (Letter from Medsafe (Chris James), 17 February 2020).
[55] APB, p 300 (Letter from Medsafe (Chris James), 17 February 2020).
[56] APB, p 317 (Letter from Medsafe to Pharmac, 19 September 2018).
[57] APB, p 322 (Letter from Medsafe to Pharmac, 21 November 2018).

may indicate a risk of reduced bioavailability and those of increased bioavailability so that urgent review could occur. In addition, they considered Pharmac should ensure that an alternative funding mechanism was available for patients who needed to switch back to their original brand.

[78] Throughout the process, Medsafe's position was that:

> … Logem is considered bioequivalent to Lamictal, but that international guidance regarding antiepileptic medicines should be considered when deciding to change the brand of lamotrigine a patient is receiving. Specifically, the fact that lamotrigine is considered a category 2 antiepileptic drug according to the MHRA guidelines, forms the basis for Medsafe's advice to date regarding lamotrigine brand switches, which is independent of a medicine's bioequivalence status.[58]

The Deceased – Cause and Circumstances of Death

[79] In this section of the Finding I will discuss the evidence given about the cause of death for each deceased and the circumstances leading up to the death (including any brand switch).

[80] It became apparent during the inquiry that establishing a cause of death in cases of epilepsy is difficult. In particular, trying to establish a direct link between a fact or incident and any subsequent seizure.

[81] During the inquest expert evidence was received from Dr Kate White, a forensic pathologist employed by the Northern Forensic Pathology Service.

[82] Dr White explained that when establishing the cause of death for a person with a history of epilepsy, the ante-mortem (before death) information is very important. She described epilepsy deaths as being "umbrella" deaths which include Sudden Unexplained Death in Epilepsy (SUDEP), *status epilepticus* and deaths arising from complications of epilepsy. SUDEP is defined as the sudden and unexpected death of a person who is known to have epilepsy, but it excludes other deaths, for example drowning or trauma (such as having a seizure and hitting their head) or *status*

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[58] APB, p 1723 (Letter from Medsafe (Chris James), 17 March 2021).

epilepticus. S*tatus epilepticus* refers to ongoing uninterrupted seizures which can result in a number of complications including body organ failure.

[83] Deaths arising from complications of epilepsy might include people who drown or have a car crash while having a seizure or who die from pneumonia after a seizure. These are described as epilepsy deaths but not SUDEP as the death results from trauma (e.g. injuries from a car crash or drowning). Then there are a group of people who have epilepsy but may die of other causes such as coronary artery disease. According to Dr White, sometimes it is difficult to establish the cause of death if an epilepsy sufferer dies suddenly. [59]

[84] Dr White also explained that a negative autopsy is where a pathologist conducts an autopsy and does not find anything to account for the cause of death. Often SUDEP findings would be the result of a negative autopsy.[60]

[85] The information gathered about the deceased was reviewed by Dr Walker, a neurologist. She has been a neurologist for 32 years and has specialised in epilepsy for that period.

The deceased individuals

Ricky Blackler

[86] Ricky was a 24-year-old scaffolder who lived with his father and sister.

[87] He had a complex medical history including a cerebral abscess as a complication of sinusitis. This required a craniotomy procedure (a surgical procedure during which part of the skull is removed) in August 2018. After this procedure he developed epilepsy and was taking Lamictal and Epilim to control seizures.

[88] According to Gary Blackler, Ricky's father, Ricky's seizures would get worse, get better, and then get worse again. He could go for two or three months without any seizures but then have "a whole lot of them. Big ones and small ones" Gary recalled

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[59] NOE Part 2, p 3.
[60] NOE Part 2, p 5.

that Ricky had been changed to the brand that had been in the news.[61] Ricky told his father that he was being trialled on different medications to "try and get the right one."[62]

[89] Ricky's pharmacy dispensing records show that he had been on Epilim (sodium valproate) from 25 September 2018. His first prescription of lamotrigine, in the form of Lamictal was on 17 May 2019. He continued on Epilim and Lamictal until 3 September 2019 when he was switched from Lamictal to Logem. [63]

[90] Gary did not notice any change in his son's health after the switch.[64] Ricky used cannabis and Gary thought that helped with his seizures. Gary's evidence was that Ricky was compliant with taking his medications.

[91] Ricky's sister, Casey, thought that Ricky's personality had changed after he was switched to Logem. She thought his seizures became worse and they were occurring more often. She also thought Ricky appeared tired most of the time and he became moody, demanding and grumpy.[65]

[92] On 4 October 2019, Ricky was at a friend's house with Casey. They got home in the early hours of Saturday 5 October 2019. According to Casey, Ricky had been drinking beer and also had some cannabis. She last saw Ricky alive about 1:15 am on 5 October 2019 and did not notice anything concerning about his behaviour or health at that time.

[93] Casey got up about 8:45 am that morning and just after 9 am, she went into Ricky's room to wake him up. He was unresponsive, and an ambulance was called. Ricky could not be revived.[66]

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[61] Blackler Bundle, p 5.
[62] Blackler Bundle, p 6.
[63] Blackler Bundle, p 14.
[64] Blackler Bundle, p 6.
[65] Blackler Bundle, p 12.
[66] Blackler Bundle, p 9.

Medical Information

[94] Ricky's neurologist was Dr Duncan from Canterbury District Health Board. He last saw Ricky on 17 May 2019 and, at that time, Ricky had had three seizures in the previous several months. Dr Duncan advises that there is some "soft evidence" that cannabis may improve epilepsy control, though this is not proven. Dr Duncan would not have expected the brand switch to cause side effects as Logem contains lamotrigine. If there was a reduced blood level due to the brand switch, he would expect this to be reflected in an increase in the number of seizures.

[95] Ricky's GP, Dr Sweeney gave evidence that Ricky's seizures were hard to control. Dr Sweeney was aware of the brand switch to Logem but cannot recall when he first learned of it. He thought it was before he last saw Ricky on 3 September 2019. Even so, he did not discuss the switch with Ricky during that appointment. He was not aware of any potential side-effects from the brand switch. Dr Sweeney thought Ricky looked "happy and well" at that last appointment.

[96] Dr Sweeney gave evidence that he usually becomes aware of drug changes from reading either Pharmac information (such as the Pharmac monthly update), or some other medical source such as communications from the Royal College of GPs, the New Zealand Medical Association or BPAC. He did not recall reading that he could have applied for funding for an extra appointment to discuss the brand switch with Ricky. He was not aware, at the time of the last appointment, that he could have made a special application to have Ricky funded to remain on Lamictal. He was also not aware that there could be side effects arising from the brand switch, so he did not discuss this with Ricky.[67] Dr Sweeney's evidence was that he was satisfied with Medsafe's advice that the medication would be the same.[68]

[97] A post-mortem examination was conducted by Dr Chris Lawrence, pathologist. In his opinion, the cause of death was SUDEP although he thought there may have been a component of positional asphyxiation as Ricky was found face down on his bed.

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[67] NOE Part 1, p 100.
[68] NOE Part 1, p 108.

[98] Cannabis was detected as part of the toxicological examination. Lamotrigine was found at a level consistent with normal use.[69]

[99] Dr Walker reviewed the information gathered about Ricky and in her opinion Ricky:

> … had focal impaired awareness seizures from his left temporal lobe due to significant structural damage following an epidural abscesses and drainage. This type of focal impaired awareness seizure is often difficult to control with medication.
>
> His Epilim was always low therapeutically and unlikely to be helpful in seizure control. The appropriate step was to add lamotrigine in a gradually increasing dose. The neurologist had instructed the patient to increase the dose up to 100mg twice daily. This had not been achieved by the patient and he remained at risk for ongoing seizures.
>
> In my opinion, the cause of the seizure was likely to be medically refractory epilepsy secondary to cerebral scarring from an abscess. The neurologist had begun a process of medication titration to improve seizure control. The prone position of the patient may have contributed to asphyxiation.
>
> The brand of lamotrigine is unlikely to have contributed as the levels did not change substantially with the switch in medications as evidenced by the post-mortem lamotrigine level, which was in the upper range of therapeutic. A deterioration in seizure control would be anticipated only if the drug levels dropped substantially after the medication brand switch.
>
> The change of brand in lamotrigine is unlikely to have contributed to the cause of death, but an association between the change of brand and death cannot be entirely excluded.

Pharmacist's evidence

[100] The brand switch occurred at Halswell Pharmacy on 3 September 2019. The pharmacist, Loren Vincent, was aware of the brand switch through the pharmaceutical schedule update, the Pharmacy Guild of New Zealand newsletter and the BPAC article mentioned earlier, titled "The funded brand of lamotrigine is changing."

[101] Ms Vincent discussed the brand switch with Ricky. He was not aware of the brand switch prior to this conversation. Ms Vincent told him that the medication would

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[69] In general, the evidence does not show when the deceased had taken their last dose, so levels found after death are not very helpful in most of the cases. ESR advises that the dose required for therapeutic effect will be different in each individual. So it is not possible to say, based on post-mortem blood level, what therapeutic effect the drug is having on an individual. APB, p1637.

look different, but the strength of medication would be the same. He asked if there was anything he should be worried about and she assured him that from the information she had received, he should not be concerned.[70]

Cause of death

[102] Ricky was first dispensed Logem on 3 September 2019. Ricky's father did not notice any change after the switch, but his sister did notice symptoms, including fatigue and moodiness.

[103] Dr Walker's evidence was that the brand switch was unlikely to have contributed to the cause of death but an association between the change of brand and the cause of death cannot be entirely excluded.

[104] Ricky's seizures had always been difficult to control so he was at risk of sudden death. His lamotrigine dose was being titrated upwards and I accept the expert evidence given that as he had not reached his optimum dose, this increased the risk of ongoing seizures. He had recently changed brand to Logem. It is difficult to exclude any of those factors from the cause of his death.

Had Ricky switched to Logem?

[105] Yes, on 3 September 2019. He died on 5 October 2019.

Did he or his next of kin know about the switch?

[106] Yes, his pharmacist discussed the switch with Ricky but:

(a) He was not advised of any possible adverse consequences of the switch by either his pharmacist or his GP.

(b) His GP was not aware of the counselling fee so did not communicate this to Ricky.

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[70] Blackler Bundle, p 1249.

(c) His GP was unaware of the special circumstances funding so did not discuss this with Ricky.

Were any changes noted after the switch?

[107] The evidence given at the inquest on this issue conflicts. Ricky's father, Gary, did not notice any changes but his sister, Casey thought his seizures were worse and his mood changed. He appeared tired.

Did Ricky express any concerns about the switch?

[108] No.

Finding

I find that Ricky Blackler, scaffolder, late of 78 Balcairn Street, Christchurch, died in his home on a 5 October 2019 from an epileptic seizure with possible asphyxiation on a background of a recent brand switch to Logem, focal impaired awareness seizures and medication dose change.

Reuben Brown

[109] Reuben was a 27-year-old agricultural worker.

[110] He had a history of poorly controlled epilepsy from childhood. Despite medication he continued to have seizures.

[111] On 17 September 2019, Reuben had a seizure and hit his head, resulting in swelling on the back of his head. There was no doctor available at the medical centre so his mother, Dellys Brown, contacted an epilepsy nurse who worked with Reuben's neurologist, Dr Wright. They then discovered that Reuben had not seen Dr Wright since July 2018 although he was supposed to see him every six to eight months. Dellys made an appointment for December 2019.

[112] Reuben changed to Logem on 19 September 2019 and had a seizure on 24 September 2019. Usually, Reuben would make a very distinctive noise in his throat

before having a seizure, but he did not do so on this occasion. Dellys was unaware of the brand switch in advance of the switch occurring.

[113] Dellys thought Reuben's seizures had been more settled during 2019. When Reuben changed to Logem on 19 September 2019, an orange sticker on the prescription bottle, advised that the brand had changed. He did not seem anxious about this.

[114] Dellys does not recall being told of any side effects from Logem but had noticed Reuben suffering from some drowsiness and short-term memory loss. However, she notes that he was on other medication as well so could not attribute the symptoms to Logem.

[115] Reuben usually took his medication 12 hours apart but had not taken it on the evening of 11 October 2019.[71] Missing a dose is a known risk factor for seizures.

[116] On 12 October 2019, Reuben's father, Campbell, asked Reuben to move a fence on the farm. Campbell later got a text message from Dellys, advising that Reuben had not come home. Campbell drove home and found the farm motorbike on the road. He could see something out in the paddock, went over and realised it was Reuben. Reuben was lying face down with his head in the grass. Campbell began CPR but Reuben could not be revived.

[117] Reuben had a complicated medication dispensing record as he went to two different pharmacies. At Turtle's Pharmacy he was dispensed Logem and at Elwyn Bates Pharmacy he was dispensed Lamictal. Records show that in 2011 when he was first prescribed lamotrigine, he was dispensed the Lamictal brand. He first received the Logem brand in December 2014. In January 2016 he went back to Lamictal but by December 2016 was being dispensed Logem. On 21 March 2019 he was dispensed Lamictal and went back to Logem on 19 September 2019.[72]

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[71] Brown Bundle, p 6
[72] Brown Bundle, p 37-41.

Medical Information

[118] In 2005 Reuben was initially seen by a paediatric neurologist, Dr Shillito. He was started on Epilim (sodium valproate) but this did not achieve complete seizure control and appears to have slowed his cognitive functions. He therefore changed to the Lamictal brand of lamotrigine but still had ongoing seizures. Dr Wright, a neurologist at Southern District Health Board, first saw Reuben in May 2009 following a referral from his GP. [73]

[119] In 2011, levetiracetam was added and Reuben came off lamotrigine completely in September 2011. However, he had ongoing seizures, so he was recommenced on a lower dose of lamotrigine and the dose was progressively increased.

[120] Dr Wright last saw Reuben in July 2018. He advises that during the time he was Reuben's neurologist, Reuben's epilepsy was difficult to control, and he did continue to have seizures.[74]

[121] A pathologist, Dr Wakefield, conducted a post-mortem examination. In Dr Wakefield's opinion, Reuben landed prone in the paddock as a result of an epileptic seizure. Dr Wakefield found pulmonary oedema and intra-alveolar haemorrhage which he advises is consistent with a hypoxic event. The finding of multiple petechiae (bleeding capillaries) would support positional asphyxia. Dr Wright gave the cause of death as positional asphyxia on a background of epilepsy. The level of lamotrigine found was consistent with normal use.

[122] Reuben attended the Catlin's Medical Centre ("the Centre"). Dr Yang, a GP at the Centre, repeated Reuben's lamotrigine prescription on 19 September 2019. He had been seeing Reuben for about three years. Dr Yang did not specify any particular brand of lamotrigine when he prescribed it and advises that he was taught to prescribe the chemical name of the medication, rather than the brand name. [75]

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[73] Brown Bundle, p 67.
[74] Brown Bundle, p 67.
[75] NOE Part 1, p 118.

[123] Dr Yang recalls being made aware of the brand switch in a communication from Wellsouth. He believes it was before he prescribed lamotrigine to Reuben on 19 September 2019. He received some information from Pharmac but cannot recall when. He explained that he tends to get information from a variety of sources including BPAC and peer discussions. He did not think the brand switch was significant and did not feel the need to discuss the brand switch with Reuben. Dr Yang was unaware of any potential complications relating to the brand switch.

[124] As Reuben's death was within four weeks of a medication change, Dr Johnstone at the Medical Centre filed a report with CARM.

[125] Dr Walker has reviewed the information held about Reuben. She noted that he had uncontrolled seizures in spite of optimal doses of medication on three anticonvulsant medications. She advises that generalised epileptic seizures occurring more than three times per year are associated with an increased risk of death, being three times the death rate of those who are seizure free, including death from asphyxiation as occurred in Reuben's case.

[126] In Dr Walker's opinion, it is unlikely that the brand switch had any significant impact on the risk of Reuben having seizures or the fact that he died from a seizure. He was known to have poorly controlled seizures and, therefore, was at high risk of having further unprovoked seizures. Dr Walker concluded that "a sudden drop, for example, forgetting a dose or two will often result in a convulsion".[76] She advises that the death was likely due to asphyxiation due to the position of Reuben's body after an epileptic seizure.

Pharmacist's evidence

[127] Reuben's dispensing records show that he started on lamotrigine (Lamictal brand) in August 2006. He changed to Levetiracetam in September 2011 and in November 2014 was prescribed lamotrigine (the Logem brand was dispensed by Turtle's pharmacy). He continued on lamotrigine and Levetiracetam and in January 2016 was dispensed Lamictal but by Bates Pharmacy.

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[76] NOE Part 2, p 259.

[128] It appears therefore that Reuben switched between Logem and Lamictal, depending on which pharmacy he visited, but was generally on Logem from December 2016 through to March 2019. He was then dispensed Lamictal until 19 September 2019, when he was dispensed Logem until the time of his death.

[129] Bates pharmacy was advised about the brand switch. This information came from Pharmac and from the BPAC article. According to Ms Taylor, pharmacist, the information received was comprehensive and was supplied in good time to allow them to prepare for the switch. The pharmacy used the BPAC article as the basis for their discussions with patients either prior to, or at the point of the brand switch. They had a discussion with each patient.

[130] Reuben was spoken to on 19 September 2019 when they first changed him to Logem. They were unaware that he had been receiving Logem previously from another pharmacy and it was their practice to dispense the same medication to epilepsy patients.

Cause of death

[131] Given Reuben's history of seizures and his intermittent use of Logem, I am not satisfied that the brand switch caused a seizure on 12 October 2019. Reuben was at risk of death from a seizure as he had uncontrolled seizures in spite of optimal doses of medication. In addition, he had missed a dose of his medication on the night before his death which increased the risk of a seizure.

Had Reuben switched to Logem?

[132] Yes, on 19 September 2019, but he had previously been prescribed Logem and switched between Logem and Lamictal several times depending on which pharmacy he attended. He died on 12 October 2019.

Did he or his next of kin know about the switch?

[133] Yes, his pharmacist discussed the switch with Reuben and there was a brand change sticker on the medication but

(a) There is no evidence that Reuben was advised of any possible adverse consequences of the switch by either his pharmacist or his GP.

(b) His GP did not discuss the counselling fee with Reuben.

(c) His GP did not discuss special circumstances funding with Reuben.

Were any changes noted after the switch?

[134] No.

Did Reuben express any concerns about the switch?

[135] No.

Finding

[136] I find that Reuben Campbell Brown, agricultural worker, late of 1447 Owaka Valley Road, Owaka, Clutha District, died on 12 October 2019. The cause of death was asphyxiation following an epileptic seizure after a missed AED dose on the evening of 11 October 2019.

Krystal Loye

[137] Krystal was a 35-year-old beneficiary. Her birth certificate records her first name as Krystle but her family advises that she was referred to as Krystal. She will be referred to as Krystal in this finding.

[138] Krystal lived with her father and had been suffering from epilepsy her whole life. She also had an intellectual disability from a young age. Krystal was not fully dependent, however she did need support for some things.

[139] Krystal's father, Gary, thought that Krystal's seizures were getting less frequent and less severe through 2018. Before her last specialist appointment in April 2019, she had been seizure free for over a year and the family wanted to reduce her medication as it made her sluggish and slow.

[140] Gary was fully involved in Krystal's health management and always attended her medical appointments. He also picked up her medication. She was compliant with taking medication.

[141] Krystal was changed to Logem in September 2019. Gary, her father, recalls Krystal's GP mentioning a brand switch during an appointment in September or October 2019 but does not recall which medication was to be switched. Gary also recalls asking the GP if it would make any difference and the GP said, "No, it's all same." Gary did not notice any changes in Krystal's condition after the brand switch. Gary also recalls that one of "the ladies" at the pharmacy mentioned the brand switch but in his view he already knew about it from the GP.

[142] Gary was not aware that he could apply for exceptional circumstances funding to go back to the previous medication and he was unaware of any potential adverse side-effects from the brand switch.

[143] Krystal's sister, Cherie, was not aware of the brand switch and she thought her sister was doing really well.

[144] Dispensing records show that Krystal was on Lamictal until 10 September 2019, when the brand was changed to Logem. She received Logem on 10 September, 7 October, 4 November, 4 December 2019 and 28 January 2020.

[145] In the early hours of the morning of 23 February 2020, Krystal's father heard a noise from Krystal's room. He went in and saw she was having a seizure. He stayed with her until she went back to sleep. About 40 minutes later, her father went back to check on her and found her deceased.

Medical information

[146] Dr Raina and Dr Beer, Pathologists, conducted a post-mortem examination of Krystal. The principal pathological findings were an enlarged heart, acute pulmonary oedema and impacted gallstone in the gallbladder neck. However, in their opinion the cause of death was unascertained, but they note that SUDEP ranges from 1.1 to 5.9

per thousand people with epilepsy (figures taken from studies of patients from 2007 to 2016). Toxicology showed lamotrigine at a level consistent with normal use.

[147] Dr Sharples is a GP at the Rotorua Medical Group Limited. Krystal was a patient there from 2002 until her death in February 2020. Krystal attended the practice regularly for medication prescriptions and medication review, largely in regard to the management of her epilepsy.

[148] Krystal's dispensing records show that she was prescribed topiramate (Topamax brand) regularly from 2010[77]. Topiramate is an anhydrase inhibitor used to treat epilepsy and migraine.

[149] Dr Sharples last reviewed Krystal on 29 October 2019, following the reduction and cessation of topiramate. This was done at the suggestion of her neurologist.

[150] Krystal had been seizure free since August 2019 when she had a seizure during a febrile gastrointestinal illness. Dr Sharples felt that this was a combination of reduced medication due to the illness and a fever. A gastrointestinal upset can affect the absorption of medication and also if there is a fever the seizure threshold can be reduced for the period of time the temperature is elevated. In his view her seizures had been well controlled for the two years prior to her death.[78]

[151] Dr Sharples does not recall discussing the brand switch with Gary and believes he (Dr Sharples) became aware of the brand switch in early 2020 (through a peer review session at his medical practice). Dr Sharples was not aware that Medsafe had recommended to Pharmac that epilepsy patients should have a GP visit or specialist appointment to discuss the brand switch.[79]

[152] Krystal's neurologist, Dr Matthew Phillips met Krystal on three occasions. On 7 June 2017, he met Krystal and her father in the outpatient clinic at Rotorua Hospital. She complained of drowsiness and she and her father wanted to make some changes. Dr Phillips decided to slowly reduce topiramate and then slowly introduce

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[77] Loye Bundle, p 10.
[78] NOE Part 1, p 41.
[79] NOE Part 1, p 41.

levetiracetam to compensate. Dr Phillips met them again on 25 October 2017 and was pleased to learn that there had been no generalised tonic clonic seizures since the medication changes.

[153] Krystal's last visit to Dr Phillips was on 10 April 2019. She had experienced no seizures at all in the previous year and had no side-effects from the prescribed drugs. Dr Phillips thought they should leave the drugs as they were given the excellent seizure control, but Gary and Krystal were keen to reduce the drugs, so they agreed on a slow reduction of the drugs, namely to reduce topiramate over four months while staying on the same doses of lamotrigine and levetiracetam. The plan was that if she had another seizure, they would increase topiramate.

[154] Dr Phillips wrote to Dr Sharples about the reduction in topiramate, with a view to stopping it in July 2019. He noted that "If she has another seizure, which is possible, please restart topiramate working up to 100mg twice a day."[80]

[155] On 29 October 2019, Krystal's general physical examination was normal. Dr Sharples prescribed lamotrigine.

[156] Dr Walker advises that, in her opinion, Krystal's death was not related to the brand switch. She notes that patients with the phenotype of generalised tonic clonic seizures only, have the highest rate of incidence of SUDEP, especially those patients who have more than three generalised seizures per year. Dr Walker also observed that the brand switch took place five months prior to Krystal's death and that the drug level of lamotrigine was relatively high post-mortem. The latter would suggest that the drop in drug level following the brand switch would be unlikely to explain the seizure. A high dose of lamotrigine would be unlikely to cause a seizure in itself, and it is not known to have cardiac toxicity.

[157] Dr Walker notes that Krystal had difficulties in controlling her seizures and had recently stopped taking topiramate. She could not say that this caused the death due to the random nature of Krystal's seizures. Dr Walker also advises that topiramate has many side-effects and many patients do not like taking it. In her view, Dr Sharples

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[80] Loye Bundle, p 38.

was correct in not reinstating topiramate after the seizure in August 2019 as there was a potential medical reason (gastrointestinal upset and fever) for that seizure.[81]

[158] In Dr Walker's opinion any seizure related to change in brand would need to be attributed to a change (i.e. a reduction) in drug level following the brand switch. This would be likely to occur within the first one to four weeks of the brand being administered.

Pharmacist's evidence

[159] Krystal's prescriptions were filled at the Western Heights pharmacy in Rotorua. Mr Monteith, pharmacist recalls receiving advice about the brand switch by way of Pharmac's regular pharmaceutical schedule update. Although Mr Monteith does not recall speaking specifically with Gary about the brand switch, the pharmacy staff were used to providing the brand switch message to other customers.

Cause of death

[160] Krystal had suffered from epilepsy her whole life. Her seizures were less severe though 2018 and her family wished to reduce her medication as it was making her sluggish and slow.

[161] The post-mortem result was an unascertained cause of death. Dr Walker's evidence was that the death was unlikely to be from the brand switch as it was four months after the switch and Krystal had a history of random seizures. Dr Walker also notes Krystal had stopped taking topiramate.

[162] I am satisfied on the balance of probabilities that the cause of Krystal's death is unascertained but probable SUDEP.

Had Krystal switched to Logem?

[163] Yes, on 10 September 2019. She died on 23 February 2020.

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[81] NOE Part 2, 234-235.

Did she or her next of kin know about the switch?

[164] Yes, Krystal's father's evidence was that he was told about a brand switch by Krystal's GP and the pharmacy but

(a) He was not advised of any possible adverse consequences of the switch by either the pharmacy or his GP.

(b) Krystal's GP did not discuss the counselling fee with him.

(c) Krystal's GP did not discuss special circumstances funding with him.

Were any changes noted after the switch?

[165] No.

Did Krystal express any concerns about the switch?

[166] No.

Finding

I find that Krystal Michelle Loye, late of 16 Tania Crescent, Rotorua, died at her home on 23 February 2020. The cause of death was unascertained, probable SUDEP.

Andre Maddock

[167] Andre was a 31-year-old assistant account manager who with lived with his partner, Nadia and their son, Lucas.

[168] Nadia's evidence was that Andre ate "clean" and was physically active. They did physical training together. In their time together she had only witnessed him having two seizures. Nadia Jooste describes these seizures as being "quite aggressive" and medium length.[82]

[82] Maddock Bundle, p 129.

[169] Nadia recalls Andre coming home with the Logem brand. It had an orange "brand change" sticker on it and Andre seemed worried. Nadia asked him whether he knew the brand was going to change and he said that he did not. They did not know about the exceptional circumstances funding.

[170] From the time Andre changed his medication to the Logem brand Nadia thought he had been very tired and "looked flat." He had mood swings and became distant.[83] He had a "massive seizure" five days after the brand switch and the seizure was about seven minutes long.

[171] Andre's work colleagues also noticed a "sharp decline" in Andre's health in the last few months before his death. He had mentioned a change in his epilepsy medication. Colleagues noticed a lack of energy, he complained of an inability to sleep, his productivity dropped and he seemed a "little off." He complained of having more seizures.

[172] Bruce, one of Andre's colleagues, sat next to Andre, in an open plan working environment. He describes Andre as alert, vibrant and full of energy. Bruce knew that Andre was an epilepsy patient. At the beginning, his health appeared good, although he did suffer from sleep deprivation from time to time. In the four to six weeks before his death, Bruce thought there was a marked deterioration in Andre's concentration span, energy levels and accuracy in his work. Bruce raised this with him and Andre said he had had a medication change and was struggling with sleep deprivation and low energy levels.

[173] Maree sat opposite Andre. She describes him as being very efficient at his work. In the period leading up to Andre's death, she noticed that he was looking very tired and asked him how he was. He told her he was on a new epilepsy drug and it was "knocking" him around.[84]

[174] About two weeks before Andre's death Nadia started seeing a noticeable change in his physical and mental behaviour.[85] Andre told his mother, Michelle in a

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[83] Maddock Bundle, p 130.
[84] NOE Part 1, p 188.
[85] NOE Part 1, p 152.

telephone call that he had started a new medication and that he had had a "massive seizure" on 11 December 2019.[86] On the night of 16 December Andre was texting with his mother and said he felt really awful.[87]

[175] Nadia advises that on 17 December 2019, they woke up as usual and had breakfast. Andre went to work and came home about 6pm. They had dinner and about 7pm Andre took their son for a bath.

[176] About 9pm Andre said, "It's coming" and had a seizure. He went to get medication he takes for seizures and took a tablet in the bathroom. The seizure lasted about 2 minutes and 45 seconds which Nadia thought was shorter than usual. She also noticed that the seizure was different than the other two she had witnessed. She describes it as being a "quiet seizure."[88] Andre was on his side on the bed and when Nadia checked on him she realised something was wrong and called an ambulance. While waiting for the ambulance Nadia started CPR.

Medical Information

[177] Andre had attended the Dodson Medical Centre since 2006 and was under the care of Dr Luke Ivancevic.

[178] Andre had a history of epilepsy, insomnia and asthma. He had his first tonic seizure on 2 March 2017 after consuming a significant amount of alcohol. He reported having two previous episodes of loss of consciousness the year before. After seeing a specialist, he was diagnosed with epilepsy.

[179] Dr Anderson is the neurologist who diagnosed Andre. He first saw him on 4 July 2017.

[180] Andre had another seizure in August 2017 and was started on sodium valproate. Despite this, he continued having seizures and levetiracetam was added. On 14 February 2018, Dr Anderson was advised that Andre had developed paranoia. That

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[86] NOE Part 1, p 155.
[87] NOE Part 1, p 156
[88] Maddock Bundle, p 129.

is a known side effect of levetiracetam so Dr Anderson advised that he should be changed to sodium valproate or lamotrigine. Andre was started on sodium valproate but continued to have seizures, so in October 2018, Dr Anderson advised he should be started on lamotrigine and tapered off sodium valproate. He wrote to Dr Ivancevic and advised that the lamotrigine should be introduced gradually and that after 8 weeks, if he was on 100mg twice daily, the dose of sodium valproate (in the form of Epilim) could be tapered off over six weeks. If he had further seizures, the dose of the lamotrigine should be increased to 150mg or 200mg twice daily.

[181] In December 2018, it was reported that Andre was off Epilim and was on lamotrigine 100mg twice daily. Andre had been seizure free for eight weeks.[89] However, in July 2019 Andre reported that he had a small seizure in June so his lamotrigine was increased to 150mg twice daily from 26 July 2019. At this stage, Dr Ivancevic was not aware of the brand switch but, generally when a generic medicine is introduced, they assume that there is no difference between the generic brand and the innovator brand[90]. Dr Ivancevic did not prescribe lamotrigine by brand and Andre was dispensed Lamictal brand 100mg tablets and Logem 50 mg tablets but was switched to Logem exclusively from 25 October 2019.

[182] Dr Ivancevic explained that he receives BPAC articles electronically but cannot recall seeing the article about the brand switch.[91]

[183] Around October 2019, the local pharmacists advised Dr Ivancevic that the brand switch was going to happen. The pharmacist, Suelji Lim thought she discussed the brand switch with Dr Ivancevic before discussing the brand switch with Andre. Towards the end of November and the beginning of December 2019, there was an article in a newspaper about the unexpected death of a patient with epilepsy and one of Dr Ivancevic's patients wanted to discuss their concerns about the brand switch with him.

[184] According to Dr Ivancevic, Andre was very strict about taking his medication.

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[90] NOE Part 1, p 161.
[91] NOE Part 1, pp 171-172.

[185] Andre called the Medical Centre on 2 December 2019, advising that he was having side effects since changing brands. Dr Ivancevic tried to call him back but thought the phone was not connected and phoned Andre's father to get Andre's number.

[186] Andre called again on 3 December 2019, advising that for two weeks he had been having constant nausea, heavy eyelids, headaches, was a bit "on edge" and "feeling generally awful." He was asked to make an appointment but declined. Dr Ivancevic was asked to call him back, but it appears this did not happen. Dr Ivancevic recalls that Andre tried to make two appointments but cancelled them. Dr Ivancevic's view is that Andre was one of the minority of patients who are more sensitive to different medications.

[187] Dr Walker notes that Andre died nearly three months after his medication was changed to generic lamotrigine.[92] His seizure control had deteriorated prior to the change and therefore, in her opinion, the connection between his death from uncontrolled seizures and the change in medication is not clear. She also notes that Andre's seizures had not been controlled on previously used antiseizure medications and therefore Andre had medically refractory epilepsy, meaning that the likelihood of a new medication fully controlling his seizures was less than 10%. In her opinion, the increase in the dose of lamotrigine, which coincided with the brand change, is the most likely explanation of Andre's increased insomnia and headache. He was also suffering from appendicitis. The poor quality of sleep is likely to have resulted in increased seizure frequency. Dr Walker also notes that the increase in lamotrigine dose may have aggravated Andre's insomnia so that may have been a reason why he was not feeling well.[93]

[188] Dr Walker ultimately concluded that the brand switch cannot be excluded as a contributor to Andre's death.[94]

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[92] In cross examination Dr Walker accepted that Andre was dispensed Logem solely from October 2019 but in her view any change would have started within a week or two of a drug switch and Andre had been on Logem prior to October 2019.
[93] NOE Part 2, p 242.
[94] Maddock Bundle, p 122.

[189] Dr Morrow, a forensic pathologist, conducted a post-mortem examination of Andre. Toxicology showed lamotrigine at a level consistent with normal use and diazepam (used to treat anxiety and control of muscle spasms). This was also found at levels consistent with normal use. The post-mortem also revealed that Andre was suffering from mild chronic appendicitis. In Dr Morrow's opinion, the cause of death was sudden death with seizure disorder (epilepsy).

[190] Dr White was asked during her evidence to comment on the cause of death provided by Dr Morrow. She advises that some pathologists use the term "sudden death" with seizure activity in a person with epilepsy but she would have termed it SUDEP.

Pharmacist's evidence

[191] Andre had his prescriptions filled at the Dodson Medical Pharmacy. Mr Lim, pharmacist, advises that he was aware of the brand switch through Pharmac and the BPAC article. Andre was on two different strengths of lamotrigine, 100mg and 50mg. He was first dispensed Logem for his 50mg tablet when the medication suppliers had exhausted stocks for Lamictal. Mr Lim told Andre he would make every effort to dispense the remaining Lamictal stock before switching him to Logem. The last Lamictal 50mg was dispensed to Andre on 26 July 2019. He was on the 100mg Lamictal until he was changed to Logem on 25 October 2019. On that date, pharmacy records note, "Spoke to Andre about his lamotrigine brand change. Dr Luke is aware of the new brand Logem and has talked to Andre about the possibility to exacerbate seizures. He has instructed Andre to call him if there are any issues with the new brand. Andre told Ms Lim that he had discussed the brand change with Dr Ivancevic. Ms Lim asked Andre whether he had any questions, but Andre replied that he was not concerned about the switch.

Cause of death

[192] The post-mortem result was SUDEP (sudden death with seizure disorder (epilepsy)). It also revealed mild chronic appendicitis. In Dr Walker's opinion the brand switch is unlikely to have contributed to the death as he had switched brands

three months earlier.[95] He also had medically refractory epilepsy. In her view, the increase of the dose of lamotrigine could have caused the insomnia and headaches. Poor quality sleep can result in increased seizure frequency. In addition, the undiagnosed appendicitis could account for some of the symptoms.

[193] It is clear that Andre was unwell in the weeks leading up to his death. This was noticed by his partner, his mother, his work colleagues and Andre himself who had telephoned the GP surgery twice complaining of symptoms including fatigue, nausea, headaches and generally feeling awful.

[194] These symptoms could be attributed to one or more of the following: the increase in the lamotrigine dose to 150mg twice a day on 26 July 2019; this could have caused insomnia which could have increased the risk of seizure; the brand switch – especially when Andre's Lamictal ran out and he was on Logem only; and the undiagnosed mild appendicitis. Given the above, it is not possible to say on the balance of probabilities what thing caused the fatal seizure, or whether it was a combination of all of the above.

Had Andre switched to Logem?

[195] Yes, on 25 October 2019. He died on 17 December 2019.

Did he or his next of kin know about the switch?

[196] Yes, Andre learned about the brand switch from his pharmacist and there was a brand switch sticker on the medication. It appears he was also made aware of the possibility of seizures being exacerbated after the brand switch.

[197] However,

(a) Andre's GP did not discuss the counselling fee with him.

(b) Andre's GP did not discuss special circumstances funding with him.

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[95] It is accepted from the evidence that Andre was on a mixture of Lamictal and Logem from 23 August 2019. He was dispensed Logem only from 25 October 2019.

Were any changes noted after the switch?

[198] Yes. His partner, mother and work colleagues noticed a decline in his health.

Did Andre express any concerns about the switch?

[199] Yes. He expressed concerns about the brand switch to his mother and also had a number of symptoms including nausea, headaches and was "generally feeling awful."

Finding

I find that Andre Maddock, assistant account manager, late of 980 Beach Road, Torbay, Auckland, died on 17 December 2019. The cause of death was SUDEP on a background of recent brand switch to Logem, insomnia, an increase in the dose of lamotrigine and mild chronic appendicitis.

William Oliver

[200] William was a 26-year-old student, doing computer studies. He developed epilepsy in his late teens. One of his brothers also suffers from epilepsy.

[201] In 2016 he was first prescribed lamotrigine and was dispensed the Arrow-Lamotrigine brand. He was dispensed Logem on one occasion on 16 January 2017 when it appears he went to a different pharmacy but, according to his partner, Elliemae, he went back to his GP and went back to Arrow-Lamotrigine. On 20 April 2019 William was dispensed Logem 25mg tablets.

[202] On 14 May 2019, William received Logem 25 mg tablets and from 18 June 2019 was dispensed Logem 100 mg. He was also prescribed phenytoin on 9 April 2019 by Dr Wilson. Dr Wilson's clinical notes do not set out the reasons for this prescription and Dr Wilson is unable to recall his reasons.

[203] On 19 July 2019, William went to the Emergency Department at Dunedin Hospital as he had developed a rash. He saw Dr Cosgrave there. Dr Cosgrave did not have access to William's GP clinical notes.

[204] In the period leading up to his death, William had suffered from some seizures. One was at home and two were at the Polytechnic he attended. His mother, Johanna reports that William used to have some warning signals of an impending seizure. These included a metal taste in his mouth and "pre-morning jerks" of his limbs. After a seizure, he would rest and sleep. She describes him as being very good at taking his medication.

[205] At one stage, William mentioned that his medications had been changed. He appeared frustrated because he did not like lamotrigine and told her it made him feel like a zombie. She was also aware that he was being weaned off clobazam.

[206] Johanna last saw William on Sunday, 11 August 2019. She came home from work briefly and William was there with his girlfriend, Elliemae. He told Johanna that he did not feel well and thought there was a seizure coming on.

[207] When she got home about 10 pm, William was not in the house, but she noticed his car parked at the front of the house. He had not eaten his dinner which she had left for him. Johanna tried calling him the next morning, 12 August 2019, but he did not answer his mobile phone and she realised his mobile phone was still in his bedroom, with his wallet. Johanna left for work about 7:20 am.

[208] Elliemae tried calling William about 8:45 am on 12 August 2019. She did not hear from him. She went over to his house and saw his car parked in its usual spot. There was an unlocked door to the house so Elliemae went into William's room to see if he was asleep. He was not there but she noticed that his wallet, phone and study material was in the room. She could not find his car keys so went out to his car and found William slumped over the foot well in the back seat of the car. He was unresponsive and Elliemae called for emergency services. William could not be revived.

[209] According to Elliemae, William smoked cannabis to alleviate his epilepsy symptoms. She recalls that he was prescribed lamotrigine and clobazam (brand name Frisium). She thought he was supposed to take the clobazam over a three-week period while he increased his Logem dose, but he had difficulty sleeping without the clobazam.

[210] Elliemae thought that William did not do as well when he was on the Logem brand of lamotrigine. He thought he had "nasty seizures" on it and it made him feel "dopey". She thought that when the medication was changed, there was a difference in his mental and physical health. He had lost a lot of weight, about 15 kg over a period of two months.[96] She described his moods as being "darker" and he appeared depressed. Elliemae also thought that when William was on Logem, it took longer for him to recover from his seizures.

Medical information

[211] Dr Mottershead was William's neurologist. He had first seen William in 2012. He last saw him on 26 July 2016. William described having had several major seizures earlier that year, so the plan was to see whether the recently introduced lamotrigine would lead to better seizure control. On 18 August 2016, an MRI brain study was performed and this had a normal result. William failed to attend his clinic appointments on 8 February 2017, 15 March 2017 and 4 December 2017. Dr Mottershead advises that recreational cannabis can exacerbate epilepsy.

[212] From mid-2017, William was a patient at High Street City Health. Dr Ozimek, a GP there advises that William used to attend for repeat prescriptions of lamotrigine. Dr Ozimek last saw William on 27 December 2018, He reported symptoms of depression so was trialled on sertraline (an antidepressant).

[213] On 27 March 2019, William went to High Street City Health and saw Dr Wilson. William told Dr Wilson that he still did not think he could work, and his mood had been tracking down. He had no thoughts of self-harm. He described himself as being easily angered and suffered from poor motivation and concentration. He said

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[96] Oliver Bundle, p 18.

he would like to try an antidepressant. William was prescribed phenytoin (an AED) and sertraline (an antidepressant).

[214] As noted above, on 19 April 2019, William went to the Emergency Department at Dunedin Hospital complaining of a rash. Dr Cosgrave was working in the Emergency Department at the time. The rash was in the context of having recently been changed to a new AED, phenytoin, even though he had previously been taking lamotrigine. A phenytoin level test was performed which showed it to be at a low level, but Dr Cosgrave was of the view that the symptoms displayed by William were most likely caused by the newly introduced phenytoin.

[215] Dr Cosgrave consulted the on-call neurologist, Dr Mottershead to seek some advice. The advice was to discontinue phenytoin and to restart on lamotrigine with a gradually increasing dose. Dr Mottershead recommended starting with a low dose of 25 mg of lamotrigine once daily and increasing it 100 mg twice daily. Dr Mottershead's evidence was that a neurologist would be unlikely to prescribe phenytoin to a young person as its side effect profile for long-term use is not very good.[97]

[216] Dr Mottershead also recommended that William be prescribed clobazam to help control the seizures while the lamotrigine dose was being increased to its normal levels. Dr Cosgrave prescribed lamotrigine (not by brand). He does not recall any discussion with William or Elliemae about William preferring the Arrow-Lamotrigine brand to the Logem brand of lamotrigine.

[217] It was Dr Cosgrave's intention that the clobazam would be used until a higher dose of lamotrigine was reached, which was intended to take about two months. His evidence was that a patient should be slowly weaned off clobazam. [98] He expected William's GP to assess how the lamotrigine titration was going and to oversee the use of clobazam. He does not recall specifically telling William that he should see his GP about that.[99]

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[97] NOE Part 2, p 16.
[98] NOE Part 1, p 142.
[99] NOE Part 1, p 143.

[218] The prescription for clobazam was for 10 mg twice daily for four weeks with two repeat prescriptions at the same dose (a total of 12 weeks).

[219] Dr Cosgrave was not aware of the brand switch until William's death was reported in the media. He does recall that in some emails he received, lamotrigine was mentioned, and he probably would have seen that Logem was considered bioequivalent to lamotrigine.

[220] After William moved from Christchurch to Dunedin, his GP was Dr Tang from the Mornington Health Centre. William first saw Dr Tang on 2 July 2019, requesting a repeat prescription of his lamotrigine, a sickness benefit certificate and a referral to a neurologist. Dr Tang wrote to Dr Mottershead, requesting a "semi-urgent" appointment for William and noting his last seizure had been in February.[100]

[221] Dr Tang last saw William on 30 July 2019 after William had presented to the Emergency Department. During that appointment, Dr Tang increased William's lamotrigine slightly to better control William's seizures and he wrote a letter to William's neurologist, noting the increase in dose and hoping to prompt an appointment. The request was noted as being "semi-urgent" as William had presented to the Emergency Department with a seizure and had had another episode in April 2019. Dr Tang was aware that William had been prescribed clobazam but did not discuss this with William. [101]

[222] When Dr Tang prescribed lamotrigine, he did not prescribe by brand. He advises that he was not told about the brand switch and, for that reason, he did not discuss any possible adverse effects with William. His evidence was that the pharmacist would usually call them if there was an issue with a brand.[102]

[223] Dr Wakefield, pathologist, conducted a post-mortem examination of William. In his opinion, the cause of death was epilepsy. He is of the opinion that William became deceased in the rear foot well of his car after suffering from a seizure. This raises the possibility of positional asphyxia. Lamotrigine was found at a level

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[100] Oliver Bundle, p 216.
[101] NOE Part 1, p 75.
[102] NOE Part 1, p 71.

consistent with normal use and clobazam was found at a level below that expected with normal use.

[224] Dr White advises that although she would have referred to the death as arising from SUDEP, the characterisation of the death being from epilepsy is not incorrect as he could have died from positional asphyxia or hypothermia (that is from a trauma so not within the definition of SUDEP).[103]

[225] Dr Mottershead thought it was unlikely that William died from the sudden stopping of clobazam or from side effects of Logem but advised:

> Well the unfortunate truth is that if someone has a history of epilepsy with generalised tonic-clonic convulsions, that's a major convulsion and there have been seizures in the most recent year then that is the biggest risk factor for having a sudden death in epilepsy. And I don't think you necessarily will find an additional cause apart from a history of epilepsy with major seizures. [...] My clinical experience does suggest that when people are stressed or miss sleep that they seem to be more vulnerable to seizures. So I wouldn't discount that possibility.[104]

[226] Dr Walker examined the information held about William. She noted the change in dispensing records from Arrow-Lamotrigine to Logem on 20 April 2019, and that over the next four months William retained good seizure control. At the same time, he was commenced on clobazam which Dr Walker advises can be very helpful in controlling seizures. Dr Walker's evidence was that withdrawal of a benzodiazepine agent such as clobazam has to be done extremely slowly as it can result in unstable seizure control. In her opinion, this is the most likely reason that the seizures became uncontrolled in the month of August.[105] Dr Walker considers it unlikely that William's change of brand had any relevance to his sudden, unexpected death as the brand switch occurred four months prior to his death and the likely provoking factor for his seizure instability was the withdrawal of clobazam. She does not believe that the cannabis use would have affected the cause of death.

[227] Dr Mottershead did not agree there needed to be a slow withdrawal of clobazam due to the low dose that William was on. William was on 10 mg twice a

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[103] NOE Part 2, p 9.
[104] NOE Part 2, p 24.
[105] NOE Part 2, pp 226-227.

day and Dr Mottershead would have recommended reducing it to once a day for a week and then stopping. Dr Mottershead referred to a study where clobazam was withdrawn from doses of 40 or 80 mg a day over a maximum of three weeks and there were no reported breakthrough seizures. In his view, it would be unlikely that a withdrawal from 10 mg twice a day would lead to poor seizure control.[106]

Pharmacist's evidence

[228] William attended Bay View pharmacy to fill his prescriptions. Ms Chang, pharmacist, advises that the pharmacy was aware of the brand switch and it was given ample time to prepare their customers for change. She advises that, as with all brand changes, they explained about the change and asked all customers to monitor themselves for "unexplained changes with their therapies". The medications are labelled with a "brand change" sticker. There is no specific record of a discussion with William.

Cause of death

[229] Expert evidence about the cause of death conflicted at the inquest. Dr Mottershead thought it unlikely that William's fatal seizure was caused by the brand switch or the stopping of clobazam. He was of the view that the most likely cause was William's history of epilepsy with major seizures.

[230] Dr Walker also considered the brand switch was unlikely to be relevant to the death as it occurred four months after William commenced on Logem. She was of the view that the clobazam should have been withdrawn slowly and stopping it suddenly may have been the provoking factor for the increase in his seizures.

[231] There is some evidence that William was weaning himself off the clobazam as he had mentioned that to his mother. However, it is impossible to know when he started that and when he finished the 12-week prescription (that is whether he took fewer tablets after a certain period of time). Given these uncertainties it is not possible to find any specific precipitating factor other than his history of epilepsy and seizures.

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[106] NOE Part 2, pp 20-22.

Had William switched to Logem?

[232] Yes, on 20 April 2019. He died on12 August 2019.

Did he or his next of kin know about the switch?

[233] Yes, he was advised by his pharmacist and there was also a brand change sticker on the medication box but

(a) There is no evidence that William was advised of any possible adverse consequences of the switch by either the pharmacy or his GP.

(b) William's GP did not discuss the counselling fee with him.

(c) William's GP did not discuss special circumstances funding with him.

Were any changes noted after the switch?

[234] Yes. His partner thought William's seizures became worse after he was switched to Logem.

Did William express any concerns about the switch?

[235] Yes. William expressed frustration about being on lamotrigine and said it made him feel like a zombie.

Finding

I find that William Oliver, student, late of 66D Neville Street, Dunedin, died of epileptic seizure with the possibility of positional asphyxia between 11 and 12 August 2019.

Jessica Reid

[236] Jessica was a 23-year-old who worked as an animal groomer at a pet store.

[237] Jessica's fiancé, Alex, had known Jessica for several years and they had been living together for five years. They were engaged for nine months. He advises that Jessica had a history of epilepsy. The year 2013 to 2014 had been the worst for seizures, with close to 10 in one year. In September 2014, they went to a neurologist in Hamilton who suggested a combination of lamotrigine and a small dose of Epilim. According to Alex, the combination worked "wonderfully" and Jessica had a couple of occasions where she was seizure-free for over a year and up to 2 and half years at the most.

[238] According to Alex, on most occasions when Jessica's antiepileptic medications were changed, they were well-informed but in 2019 they did not get any warning about the brand switch. He thought, "mood wise "Jessica was really good for the last six months of her life. They had just bought their first house together. Healthwise, she appeared constantly tired and suffered from headaches.

[239] Jessica's mother, Karen recalls that Jessica was on Logem in 2019 but in June she was given Lamictal by the pharmacy. Jessica complained of side-effects from the Lamictal including headaches and feeling generally unwell. She had her first seizure after two and a half years on 27 July 2019.

[240] On 19 September 2019, Jessica had been working as usual as a pet groomer. The assistant manager, Jamie, did not notice anything unusual about her that day.

[241] On 19 September 2019, Alex and Jessica went to bed about 10 pm. Alex got up early the next morning and he left for work about 6:40 am. Jessica was awake at that time.

[242] Jessica's dispensing records show that she started taking lamotrigine in August 2012. In May 2015 she started on the brand Logem but on 16 August 2017 was given the brand Lamictal by the Unichem Russell Street pharmacy. On 7 August 2018, she restarted on Logem which was issued by the Unichem Munro Street pharmacy. The dispensing records show that on 22 June, 27 July and 26 August 2019 she was given the Lamictal brand. However, the 26 August entry was clarified by the pharmacist as being an error as Jessica was given Logem on that day.

Medical Information

[243] Dr Triggs, a forensic pathology registrar conducted a post-mortem examination of Jessica under the supervision of Dr Kate White. Lamotrigine was confirmed at a level consistent with normal use. The post-mortem examination showed no injuries or natural disease which could have contributed to or caused the death. In Dr Triggs' opinion, the cause of death was SUDEP.

[244] Jessica was a patient at The Doctors, Napier since 2011. She saw several doctors at that practice. In February 2019, Jessica requested a repeat prescription of her medications. Dr Goodwin from The Doctors asked her to come in for a review as it had been a year since she had last seen her. Jessica was "annoyed" about this as she felt her neurologist was monitoring her epilepsy. Dr Goodwin telephoned her and issued the prescription but also explained why she needed to be reviewed. In June 2019, she requested a further prescription via "Manage my Health". Dr Goodwin was aware that Jessica would likely have a brand change but thought the pharmacist would discuss this with her.

[245] Dr Goodwin last saw Jessica on 26 August 2019. Jessica appeared well and they did not specifically discussed medications. Her lamotrigine level was checked in September 2019 and was within the expected range.

[246] Jessica was being treated for her epilepsy by Dr Jones, SMO neurology at Hawkes Bay District Health Board. He advises that as of 2015, seizures were very well-controlled by adding a small dose of Epilim. She had a seizure in November 2015 triggered by sleep deprivation and a seizure in September 2018 possibly triggered by drinking a different type of alcohol than she was used to. She saw a neurologist in December 2018 and told the neurologist that after that incident, she had decided to discontinue Epilim as she often forgot to take it at night. As she had remained seizure free on a very low dose the neurologist considered she would do well on lamotrigine alone. Dr Goodwin was advised that if Jessica's migraines continued, or if she had further seizures, she should be prescribed topiramate.

[247] Dr Jones was not aware that Jessica's lamotrigine brands were being switched from Logem to Lamictal and back again.

[248] Dr Walker reviewed the information collected about Jessica. She notes that Jessica seizures were under good control with the addition of a small dose of Epilim. She also notes that Jessica elected to stop taking Epilim in the 12 months prior to her death. Once she stopped taking Epilim, the blood levels of lamotrigine dropped substantially. Dr Walker advises that this is an expected pharmacokinetic consequence of the interaction between the two drugs.

[249] Dr Walker notes that Jessica was taking Lamictal in the three months prior to her death. Therefore, the introduction of Logem, which occurred 14 months prior to her death, cannot be implicated in the cause of death.[107] She is also of the opinion that the change back to Lamictal, three months prior to her death, cannot be implicated. In her opinion, the most likely cause of the seizure which resulted in Jessica's death was the withdrawal of Epilim.

Pharmacists' evidence

[250] Mr Mclean-Smith is the manager and a pharmacist at Unichem Munroe Street. He advises that Jessica began visiting the pharmacy in 2013. She initially took the Mogine brand, but this was discontinued in 2015 and she changed to Logem. Mr Mclean-Smith was not aware that Jessica was receiving another brand from a different pharmacy. The pharmacy did receive information from Pharmac in April 2019 regarding the brand switch.

[251] Russell Street pharmacy's records show that Jessica had been on Lamictal from August 2017 and she had regular repeat prescriptions until July 2018. On 9 April 2019, she came to the pharmacy requesting an emergency supply as her medication had run out. They confirmed with her that she was on Lamictal and dispensed that brand. She subsequently received Lamictal on 22 June 2019 and 27 July 2019. As stated above, on 26 August 2019, she received Logem,

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[107] Note that Jessica was dispensed Logem in August 2019.

[252] Russell Street pharmacy was aware of the brand switch from information they received from Pharmac and the local District Health Board. They began to transition their patients from Lamictal to Logem in August 2019. This was a two-stage process involving orally advising patients of the brand switch and putting a brand switch label on the medication. They advised patients of the risks and benefits of changing brand and that loss of seizure control was unlikely to be an issue.

[253] Jessica's sister, Hannah, advises that Jessica visited the Unichem pharmacies in Hastings as well as in Napier, assuming that because the two pharmacies were both Unichem pharmacies, their systems would be linked. As far as Hannah is aware, no pharmacist discussed the brand switch with Jessica.

Cause of death

[254] Jessica was another person who received different brands of lamotrigine, depending on which pharmacy she visited. She was dispensed Logem on a couple of occasions in 2015 and then pretty consistently until August 2017 when she was dispensed Lamictal. She was generally on Lamictal until 7 August 2018, when she was given Logem. Jessica also took Epilim and this combination of lamotrigine and Epilim worked well but Jessica decided to stop taking Epilim about 12 months before her death. Dr Walker notes that stopping the Epilim would have meant the levels of lamotrigine would drop substantially due to an expected pharmacokinetic consequence. Dr Walker believes that the likely cause of the seizure that caused Jessica's death was from withdrawal of Epilim.

[255] Given Jessica had been well on Logem previously, I agree with Dr Walker that the switch from Logem to Lamictal and back again would be an unlikely trigger for the cause of her death.

[256] I am satisfied on the balance of probabilities that the cause of Jessica's death was SUDEP.

Had Jessica switched to Logem?

[257] Jessica went to two pharmacies and received both Logem and the Lamictal brand of lamotrigine intermittently. She received Logem on 26 August 2019. She died on 20 September 2019.

Did she or her next of kin know about the switch?

[258] Yes, according to Jessica's pharmacies, they explained the brand switch to patients and also put a brand switch sticker on the medication box but

(a) There is no evidence that Jessica was advised of possible adverse consequences of the switch by her GP and the pharmacist relied on the Pharmac advice that loss of seizure control was unlikely to be an issue

(b) Jessica's GP did not discuss the counselling fee with her.

(c) Jessica's GP did not discuss special circumstances funding with her.

Were any changes noted after the switch?

[259] Jessica did express a dislike of the Lamictal brand and her partner thought she appeared tired and suffered from headaches during the last six months of her life.

Did Jessica express any concerns about the switch?

[260] No.

Finding

I find that Jessica Louise Reid, animal groomer, late of 303 Frederick Street, Hastings, died on 20 September 2019. The cause of death was SUDEP.

Other Expert Evidence Given During the Inquest

Jane Hanna

[261] Jane Hanna founded an organisation in the United Kingdom called SUDEP Action. She has been awarded an OBE for her work in tackling epilepsy mortality.

[262] Ms Hanna advises that National Clinical Guidelines developed in the UK in 2004 are underpinned by a fundamental requirement of decision-making in partnership between the patient and the clinician:

> Person-centred prescribing and medicines management is the most effective first line intervention to keep patients safe. Given epilepsy is a high-risk condition when known risks of sudden death can worsen it is extremely problematic if the patient does not know about epilepsy and risk including SUDEP and may not understand the implications of any medication change. This underlies the need for clinical involvement of a professional who understands the clinical history and has full access to medical notes.[108]

[263] Ms Hanna referred to the UK MHRA a Drug Safety Update volume 11, issue four; November 2017: 5 which states in relation to AEDs that, "differences between alternative products (for example, product name, packaging, appearance, and taste) may be perceived negatively by patients and/or carers, and may lead to dissatisfaction, anxiety, confusion, dosing errors and reduced adherence. In addition, difficulties for patients with comorbid autism, mental health problems, or learning disability should also be considered."[109]

[264] Between 2010 and 2018 a partnership with SUDEP Action and researchers and clinicians in Cornwall found that person centred communication of risk using a SUDEP and seizure safety checklist as a safety tool not only increased implementation of guidelines on communication from 10% to 80% but enhanced understanding of risk which was shown to reduce risk. The checklist and the digital EpsMon App for people with epilepsy is now recognised as best practice for taking a risk management approach to epilepsy.[110]

[265] The checklist summarises 18 factors identified through research as having an increased risk of SUDEP or epilepsy seizure. The checklist takes about 10 minutes to

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[108] APB, pp 530-531 (Jane Hanna Statement, 21 July 2020, para 8).
[109] APB, p 532 (Jane Hanna Statement, 21 July 2020, para 10).
[110] APB, p 535 Jane Hanna Statement, 21 July 2020, para 18).

complete with a patient during an initial consultation or a regular check-up. It can also be used at other key appointments where a patient becomes unstable or medication changes are being considered.[111] The EpsMon App is a 10-minute review which aids a patient to be aware of how person-centred risks are improving or worsening with advice on seeking help.[112]

[266] Ms Hanna believes that given death can result from a sudden seizure relapse, a precautionary approach would be fundamental to any regulatory or decision-making relating to the switching of products for people with epilepsy. Patients who are switched should be given a warning that they could experience a relapse or worsening of seizures or side-effects and that they have the right to ask for the involvement of their prescriber and to be supported to make the case for consistency of supply for reasons of person-centred patient safety.[113]

[267] Ms Hanna was critical of the patient leaflet distributed by Pharmac as although it referred to patients raising any concerns, there was no information in the leaflet about the risk that some people may experience symptoms as a consequence of a brand switch. She also thought that the subcommittee's concern that placing too much emphasis on the change could cause anxiety was a very paternalistic approach to people with epilepsy and their families. [114]

Associate Professor Medlicott

[268] Associate Professor Medlicott is an academic pharmacist with research and teaching experience in drug delivery, drug analysis and pharmacokinetics.

[269] In her evidence, she explains that bioequivalence is based on the pharmacokinetics of the medicinal product. Pharmacokinetics comprises the dose – concentration relationship and the pharmacodynamics comprises concentration – effect (efficacy and toxicity) relationship of a drug. The requirements for similarity in pharmacokinetics defined by Medsafe ensures sufficient similarity between brands. Associate Professor Medlicott also notes that bioequivalent medicines may contain

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[111] APB, p 1555 (Jane Hanna Supplementary Statement, 16 February 2021, para 7).
[112] APB, p 1559 (Jane Hanna Supplementary Statement, 16 February 2021, para 10).
[113] APB, p 1560 (Jane Hanna Supplementary Statement, 16 February 2021, para 13).
[114] NOE Part 2, pp 79-80.

different excipients. The batches of the test product used in bioequivalence studies must meet defined requirements to minimise the risk of differences occurring between the batch used in testing and subsequent batches used in patients. When there is a strong relationship between drug pharmacokinetics and drug effect(s), ensuring similar pharmacokinetic parameters should mean the pharmacodynamic effects are sufficiently similar to allow safe interchange of bioequivalent brands.[115]

[270] Associate Professor Medlicott has reviewed the Study and is of the opinion that it is well designed, a good study with a sufficient number of subjects. She notes that the study was not designed to look at individual responses. The subjects in the study received the reference product only once so the Study does not show how variable the response to either one of the products is in an individual, which makes comparing the change between the brand and the reference more difficult to interpret because of the one-off measurement.

[271] Bioequivalence studies are conducted on healthy volunteers because the study is designed to remove the variability that may exist in a group of patients with epilepsy.[116]

Dr Walker

[272] As well as commenting on each individual deceased, Dr Walker was asked general questions in relation to epilepsy medications and deaths caused by epilepsy.

[273] In her view, in relation to SUDEP, it is often difficult to ascertain the cause of death but there are clear risk factors for SUDEP with patients who have generalised convulsive seizures at a rate of more than three per year. There is an indication in some of the papers that there is an increased risk in patients who change medications frequently, but often the reasons they are changing medications frequently is that they have poorly controlled epilepsy. In other words, it is not changing brands that has caused the seizure, but they are at greater risk of having seizures and therefore at greater risk of SUDEP.[117]

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[115] APB, pp 519 – 520 (Associate Professor Natalie Medlicott Report, 28 May 2020).
[116] NOE Part 2, pp 191 – 199.
[117] NOE Part 2, pp 216-217.

Andrew Gaudin

[274] Mr Gaudin is the Chief Executive of the Pharmacy Guild of New Zealand (the Guild). The Guild represents the majority of community pharmacy owners. Mr Gaudin's evidence was that the Guild opposed the brand switch due to concern for the vulnerable patients affected by epilepsy and bipolar disorder and reports from their members of problems and negative experiences in relation to earlier brand switches affecting these patients. The Guild informed their members about the brand switch in their weekly E newsletter. They also direct their members to information and resources on the Pharmac website.

[275] Mr Gaudin advised that his members have both a professional expectation and a contractual obligation to inform patients about brand switches and the pharmacist will often say that if the patient has any concerns about the new brand or experiences any side-effects, they should speak to their GP.

[276] Mr Gaudin's evidence was that not all pharmacies have a linked practice management system so they are not in a position to know what other pharmacies have dispensed to patients. Under the HealthOne system in the South Island, there is an ability to share dispensing information. There is a similar system in the northern region called TestSafe. TestSafe and HealthOne cannot communicate with each other.

[277] Mr Gaudin referred to the New Zealand Electronic Prescription Service that collects information about all prescriptions from pharmacies but does not provide the information to pharmacies. He concludes that there is no "single one joined up IT health system that has all of the dispensing data available for use by community pharmacies."[118]

[278] The Guild had suggested to DHBs during the implementation of the brand switch that the patient management system could be altered to remind pharmacists to discuss the brand switch with the patient. This suggestion was not implemented.

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[118] NOE Part 2, p 291.

Dr Sharpe

[279] Dr Sharpe is a paediatric neurologist at Starship Children's Hospital. Most of her work is with children with epilepsy. She has had no involvement with the six deceased who are the subject of this inquest.

[280] Dr Sharpe has had many patients who have reported adverse side-effects since the brand switch. In her opinion, New Zealand has no system to monitor therapeutic non-equivalence of drugs and therefore the brand switch cannot be discounted as the cause of death in the six cases.[119]

[281] Dr Sharpe has reviewed the Study and is of the view that although the study demonstrates that Logem meets the criteria for bioequivalence, the same data also shows Logem is not necessarily therapeutically equivalent to Lamictal for individual patients. In the study, 24 volunteers are given a single dose of Lamictal and had serial plasma levels determined. The same individuals were given a single dose of Logem and had serial plasma levels determined. She notes that the Study shows that three of the 24 subjects had substantially higher peak serum levels following a Logem dose compared to a Lamictal dose; four of the 24 subjects had substantially lower trough serum levels following the Logem dose and 13 of the 24 subjects at the change of more than 10% in their AUC values.[120] Dr Sharpe's evidence is that seizure control depends on maintaining at all times a patient specific minimum serum level of the protective medication and that intolerable side effects, such as headache, nausea, dizziness, ataxia, irritability or blurred vision, may occur if too high a serum level is reached.[121]

[282] Patients subject to substantial decreases in the trough levels would be at risk of seizure relapse.[122] Dr Sharpe also advises that if she had seen the bioequivalence report earlier, she would have given different advice to her patients, namely, she would have established their individual therapeutic trough levels prior to the switch and re-checked that after the switch to protect against seizure relapse.[123]

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[119] APB, pp 522-523 (Dr Cynthia Sharpe Statement, 15 June 2020, para 6).
[120] Area Under the Curve.
[121] APB, pp 1452-1453 (Dr Cynthia Sharpe Supplementary Statement, 9 February 2021, paras 11, 13).
[122] APB, p 1453 (Dr Cynthia Sharpe Supplementary Statement, 9 February 2021, para 13).
[123] APB, p 1454 (Dr Cynthia Sharpe Supplementary Statement, 9 February 2021, para 19).

[283] Of the patients she treated, she put in around 30 applications for exceptional funding. She advises that a third of them were anxious about the brand switch, about a third of them had been experiencing side-effects and another third had a seizure breakthrough.[124]

[284] Dr Sharpe concluded that she would like to see a system that monitors brand switches including an audit at the beginning of the rollout of the brand switch and an audit of the rates of loss of efficacy and the occurrence of intolerable side effects.[125]

Responses to Dr Sharpe's evidence

[285] Professor Glue is a professor of psychological medicine at the University of Chicago and a consultant psychiatrist with the Southern District Health Board. He has 34 years of clinical pharmacology and psychopharmacology research and advanced teaching experience in the United States, the United Kingdom and New Zealand in clinical, academic and industrial settings. He has been involved in over 100 clinical trials and in previous roles worked on clinical trials for antiepileptic drugs. He has run or reviewed hundreds of bioequivalent studies for a range of medications.[126]

[286] At the request of Mylan, Professor Glue reviewed the Study. In his view, the study was appropriately designed, analysed and reported. It is consistent with the most recent international guidance on design and execution of bioequivalence studies. He notes that the minimum number of subjects for any bioequivalence study is 12 and is of the view that 24 subjects would provide adequate statistical power. In his view, bioequivalence was clearly demonstrated between Lamictal and Logem.

[287] Professor Glue's evidence was that it was not possible to compare individual patient data from an average bioequivalence study and to draw the conclusions that were drawn by Dr Sharpe, as a different study design would be needed to test for individual bioequivalence, such as a four-period study design in which both formulations were administered twice to the same subject.[127]

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[124] NOE Vol 2, p 283.
[125] NOE Part 2, p 275.
[126] APB, p 1652 (Professor Paul Glue Statement, 3 March 2021, para 6).
[127] APB, p 1654 (Professor Paul Glue Statement, 3 March 2021, para 17).

[288] Mr James, the group manager for Medsafe, notes that the Study, like all bioequivalence studies, was designed to show that a new patient starting on a lamotrigine containing medicine should expect the same safety and efficacy profile whether taking Logem or Lamictal. The study was not designed to show whether a patient already stable on a particular brand could safely switch to taking a different brand and was not designed to show the therapeutic equivalence of the two brands for individual patients.

[289] Dr Walker's response is that with regard to the association of adverse effects with a brand change, a new level will stabilise in one week. Studies on brand changes have taken eight weeks as the longest time to study adverse effects from drug substitution. In her opinion, any event after this time cannot be assumed to result from the change in brand. In her experience, adverse responses to drug change usually occur within a week or two after the change. If a seizure occurs due to a missed dose, it usually happens within 24 hours of the missed dose.[128]

[290] Dr Walker's evidence was that in the clinical care of patients, not a great deal of notice is taken of the drug levels because the levels do not correlate directly with therapeutic seizure control. It is known that patient drug levels will vary quite substantially but adherence to medication is likely to cause a much greater variation in drug levels than 10% shown in the Study. Therefore, in Dr Walker's view, a small variation from generic to a standard drug is probably not necessarily clinically relevant compared to the fluctuations that normally happen in a given patient over a period of time.[129] As noted above, Dr Walker also referred to research which concludes that the only clear risk factors for SUDEP were patients who had generalised convulsive seizures at a rate of more than three per year.[130]

Discussion of Issues

[291] Many of the issues identified for the inquest have been answered by the largely uncontested evidence referred to in detail above. This includes the steps taken by Pharmac to implement the brand switch.

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[128] APB, p 1721 (Email from Dr Walker, 11 March 2021).
[129] NOE Part 2, p 217.
[130] NOE Part 2, p 216.

[292] What follows is a discussion of the issues that remain.

Issues continued – steps taken by Pharmac

[293] I do not intend to set out the steps taken by Pharmac to approve and implement the brand switch as they appear elsewhere in this finding. However, there are some aspects of the steps taken that require further discussion.

Was Logem bioequivalent to the brands it replaced?

[294] The expert witnesses were in agreement that Logem is bioequivalent to Lamictal. The majority of the experts were also of the view that the Study complied with international guidance and was appropriately designed and reported.

[295] I accept that evidence and find that Logem is bioequivalent to the brands it replaced and that the Study was fit for purpose and could be relied upon to establish bioequivalence.

Apart from reports to CARM, is there any other national system of monitoring generic medications to determine therapeutic equivalence and if not, should there be?

[296] The majority of experts were clear that the Study was not suitable to establish whether or not Logem is therapeutically equivalent to Lamictal.

[297] Dr Sharpe's evidence was that in the treatment of epilepsy, the medication dose is increased until either seizures are in remission, or intolerable side effects occur. She explained this means that seizure control depends on maintaining, at all times, a patient-specific minimum serum level.[131]

[298] Although Dr Sharpe drew some conclusions about therapeutic equivalence from the Study, I prefer the evidence of Professor Glue that is it not possible to compare individual patient data from an average bioequivalence study and to draw the conclusions Dr Sharpe did because the Study's data do not permit this.[132] He explains that a key aspect of individual bioequivalence is assessment of intraindividual variance

[131] APB, p 1452 (Dr Cynthia Sharpe Supplementary Statement, 9 February 2021, para 11).
[132] APB, p 1654 (Professor Paul Glue Statement, 3 March 2021, para 17).

in a bioavailability metric to evaluate tests and reference product metrics within each individual as well as in the population.

[299] I also accept Dr Walker's evidence about the normal variability of drug levels within individuals.

[300] Apart from therapeutic equivalence studies, there were other channels available to Pharmac and Medsafe to receive adverse reports about drugs. Pharmac receives the minutes of the Medsafe Adverse Reaction Committee and these minutes can contain information about adverse drug reports. Hospital admissions can be monitored. Members of the subcommittees who are GPs may report adverse reactions in their patients to other members of the subcommittees.[133]

[301] However, there was no specific study in place to monitor the therapeutic equivalence of Logem to Lamictal and nor was there a legal requirement to have one.

[302] One possibility would have been to monitor serum levels in patients before and after the brand switch. This could have been done for a sample group of patients or for every person subject to the brand switch. There was some evidence given about the costs of such a study. Given my findings on the causes of death – that is that none of the six deaths can be attributed solely to the brand switch, it is not within the scope of this finding to decide whether there should have been such a study in this case. However, I agree with Dr Sharpe that given the vulnerabilities of patients with epilepsy, such monitoring could have been valuable to provide confidence (or not) to consumers and prescribers.

[303] I intend to refer this finding to the Ministry of Health for consideration of this issue for brand switches in the future.

What advice was given to prescribers?

[304] Pharmac's evidence was that it:

> … would look to engage with health professionals by providing information about support for brand changes, bioequivalence and [their] Exceptional

[133] NOE Part 2, pp 182-183.

> Circumstances Framework through their representative college/organisation. Pharmac would also apply a brand switch fee for pharmacists, reimburse general practice appointment fees and develop targeted communications for healthcare professionals.[134]

[305] Pharmac contracted with BPAC to provide an article about the brand switch. The article was published on 22 August.[135] BPAC articles are sent electronically to more than 4,000 GPs, almost 1000 other doctors and 1,500 pharmacists, amongst others.[136]

[306] The BPAC article stated that, "Counselling in general practices and pharmacies is imperative to talk through any concerns patients may have about changing brands of medicines and to provide reassurance that their tablets may look different they are still receiving the same medication. "[137]

[307] The article referred to the counselling fee and the special circumstances funding available and contained a section on changing patients to another brand of lamotrigine. This included advice that, "Generic medicines are designated as bioequivalent and contain the same dose of active ingredient, however, it is possible that some patients will absorb a slightly lower or higher amount of medicine when they change to a different brand due to slight differences in bioavailability which are within the accepted margin of error. Although unlikely this could result in clinical symptoms."

[308] The possible clinical symptoms referred to in the BPAC article included headache, nausea, tremor, dizziness, irritability, blurred vision, seizures, myoclonic jerks and mood instability.

[309] Evidence received during the inquiry shows that there were also communications sent out to prescribers from a variety of organisations including the New Zealand Medical Association regarding the waived GP co-payment fee and [138]

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[134] APB, p 1498 (Lisa Williams Brief, 5 February 2021, para 4.14).
[135] APB, p 1536 (Lisa Williams Brief, 5 February 2021, Schedule 6).
[136] APB, pp 1519-1520 (Lisa Williams Brief, 5 February 2021, para 5.69).
[137] APB, p 539 (BPAC Article); published on https://bpac.org.nz/2019/lamotrigine.
[138] APB, pp 595-596 (NZMA Newsletter).

exceptional funding claims,[139] and The Royal College of General Practitioners about the brand switch.[140] Other organisations, such as WellSouth, could find no record of communications with prescribers about the brand switch.[141]

[310] It became apparent during the inquest that GPs receive information in a wide variety of ways. It also became apparent that many of the messages about the brand switch were not received by GP's or if received, were not retained so that they were easily recalled when a patient with epilepsy was seen at the time of the brand switch.

[311] Although GPs prescribe medicines like lamotrigine by the chemical name, they should be informed of brand switches so that they can have informed discussions with their patients. That is supported by the BPAC article referred to above. None of the doctors who gave evidence knew they could claim a counselling fee to have an appointment with their patient to discuss the brand switch. None of them discussed the exceptional circumstances funding with the deceased. None of them discussed possible symptoms with their patients.

[312] Pharmac accepted that a minority of patients may not have coped well with the brand switch.[142] Given that, in my view, it was necessary for Pharmac to ensure that GP's were well prepared for the brand switch. I accept Pharmac's submission at the inquest that there is a joint responsibility in the health sector – so that GPs and pharmacists have a responsibility to keep up to date with information produced by organisations such as Pharmac[143]. Ms Williams from Pharmac accepted that in future, strategies such as having an electronic means of communication for high impact changes or conducting some sort of market research or auditing of a sample of GPs to ensure the important messages had been received were worth considering.

[313] In my view, the advice distributed by Pharmac in relation to the brand switch was sufficient to ensure that GPs had sufficient information to have an informed discussion with their patients. However, Pharmac had no procedures in place to ensure

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[139] APB, p 614 (NZMA Communications).
[140] APB, p 621 (The Royal College of General Practitioners Newsletter).
[141] APB, p 618 (Email from WellSouth).
[142] NOE Part 2, pp 92-93.
[143] NOE Part 2, p 96.

that its methods of communication were effective. This, in my view, resulted in a lack of informed discussion with the patients.

What advice was given to pharmacists?

[314] The pharmacists involved in this inquiry were all advised of the brand switch through such publications as the Pharmaceutical Schedule Update, the Pharmacy Guild of NZ newsletter and the BPAC article.

[315] The evidence was they had brand switch conversations with all the patients, although some did not make a written record of the conversions.

[316] The reason pharmacists were more informed about the brand switch than GPs was probably due to their professional and contractual obligations to inform patients about any brand switch. That is, pharmacists are alert to brand switches and the obligations those brand switches place on them. To that extent the information provided by Pharmac worked well to inform pharmacists about the upcoming switch.

[317] There was no evidence given that the pharmacists discussed specific adverse symptoms with their patients or the GP co-payment or the exceptional circumstances funding. Some general information was given that if they had concerns they should contact their GP and one pharmacist explained that loss of seizure control was unlikely. The family members and partners who gave evidence were not aware of the exceptional circumstances funding or the GP co-payment.

[318] I am of the view that Pharmac's communication strategy was lacking to the extent there was confusion over who was to deliver the key messages. Pharmacists delivered the brand switch message, but important messages such as the counselling fee, symptoms to be aware of and the exceptional circumstances funding available did not reach patients. Many GPs thought pharmacists would deliver the brand switch message.

How was the switch communicated to consumers?

[319] As discussed above, messages about the brand switch were delivered by pharmacists and some GPs. As I have already noted, I have found those messages were lacking in some crucial areas.

[320] I note that Dr Coates, in his report, commented on the lack of preliminary consultation Pharmac had with its own Consumer Advisory Committee (CAC). He considers the CAC's input would have been useful and involving it would have been good practice.[144]

[321] There is no evidence that any of the deceased received the pamphlet produced by Pharmac for consumers, but I note that, even if they had received the pamphlet, it did not alert consumers to the possibility of any adverse symptoms from the brand switch. Instead, the pamphlet read:

> Logem has the same active ingredient as the other brands and is delivered to the body in the same way. This means your new brand of medicine works the same as your old brand. You shouldn't notice any difference in how it affects you.

[322] The pamphlet did not mention the exceptional circumstances funding but instead advised consumers who wanted to keep their current brand to ask the pharmacist to check the price and availability.

[323] The pamphlet did not mention the co-payment funding but instead suggested the consumer talk to their healthcare professional.[145]

[324] In my view, the pamphlet was insufficient for its purpose of giving relevant information to consumers.

Recommendations and Comments

[325] Under s57A of the Coroners Act a coroner may make recommendations of comments in the course of, or as part of the findings of, an inquiry into a death. The

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[144] APB, p 464 (Independent Review of Pharmac's Lamotrigine Sole Supply Decision, Dr Jonathan Coates, 12 May 2020, para 2.2).
[145] APB, p 1533 (Pharmac pamphlet).

recommendation or comment must be clearly linked to the factors that contributed to the death to which the inquiry relates.

[326] Given my findings on the causes of death for the six deceased, I am unable to make any recommendations or comments as the evidence does not clearly link the brand switch to the seizures that led to the deaths.

[327] However, to summarise some useful observations which have arisen during the inquiry I note:

(a) For patients with epilepsy, risk awareness, risk assessment and risk mitigation are essential features of managing the condition. This requires a high level of communication between a patient and their health professionals.

(b) Research in the UK shows that a patient-focused approach lowers risk for epilepsy patients, and this should include open discussion about the risks of SUDEP and possible side effects from medication changes.

(c) One of the purposes of the brand switch was to stop inadvertent brand switching by pharmacies who are unable to access a patient's dispensing history. A national dispensing database available to all pharmacists would allow pharmacists to check brands before dispensing.

(d) There was no evidence that the deceased were advised of the counselling fee, exceptional circumstances funding or specific adverse symptoms that might arise. There was a lack of understanding about who was responsible for providing such information to the deceased.

(e) Communications with epilepsy patients can be improved by tools such as the Seizure Safety Checklist and the EpsMon App used in the UK. Such tools could be of great assistance to GPs and patients when brand switches occur.

(f) Random audits of prescribers or an electronic means of communication for high impact brand switches may ensure that important messages have been received and understood.

(g) There is no formal system in New Zealand to comprehensively monitor therapeutic equivalence between different brands of drugs.

Restrictions on Publication

[328] Pursuant to section 74 of the Coroners Act 2006, I am satisfied it is in the interests of decency or personal privacy to prohibit the making public of photographs of the deceased taken by police.

Judge D Marshall, Chief Coroner