Lamotrigine Implementation Project Team

Meeting held 12 August 2019

Attendees: Adam McRae, Implementation Lead and Project Manager
Adrienne Martin, Therapeutic Group Manager Neurology
Andrew Oliver, Therapeutic Group Manager Neurology 2nd
Hannah Tibble-Gotz, Customer Support and Enquiries Management
Laura Baker, Funding Coordinator
Peter Murray, Deputy Medical Director
Vikki Carter, Senior Communications Adviser

MINUTE

	Subject	**Reference**

1. **Review of minutes from 12 August:**

Noted the following actions that:

- Contingency plan had been approved by DOO with clarity that the serious adverse event checklist is to be completed when events were reported directly to PHARMAC (not 3rd party reports such as those to CARM)

  Serious adverse event checklist had been approved by DOO

  NPPA staff and enquires team have been briefed on the checklist and encouraged to complete at least initial information if the TGM is not available

  Restrictions had been set on the Objective folder where completed check lists are to be stored as these contain patient information

- Investigation into placing the numbers of applications and outcome on the PHARMAC web site (in a separate area so as not to be confused with NPPA) was outstanding and would be followed up by Vikki

  Noted that work continued on the bpac article.

2 **Serious adverse event checklist:**

Noted that no adverse events had been reported 'first hand' to PHARMAC.

3 **Update on EC applications:**

There have now been 14 exceptional circumstances applications, 3 approved, 2 withdrawn, 2 where a trial of Logem was considered appropriate and 7 under assessment

Continue to consider if there was potential to include key themes around applications that were not successful to guide clinicians. This will become clear if/as we receive more applications

[redacted] (member of Neurological Subcommittee and on panel examining lamotrigine EC applications) has been approached by media for comment around the brand switch Laura and Vikki to follow up to provide key messages to Paul and note any comment would be in his own capacity not as a representative of PHARMAC and any patient specific information in relation to any exceptional circumstances applications needed to remain confidential.

4. **Communications update:**

Noted that there had been no media enquires since last meeting

One ministerial in relation to availability of Lamictal brand at a pharmacy level (Louise Upton, Taupo Electorate) Noted that pharmacies would be managing stocks of Lamictal in anticipation of significantly reduced volumes and confirmed GSK has made a clear undertaking to continue to supply. Adam has provided some background VC coordinating response.

An e-mail from [redacted] has been sent to Prime Minister, Minister of Health and Associate Minister expressing significant concern about the safety of the brand change. This has been responded to.

A letter from [redacted] to CAC has been received Simon will lead the drafting of a response. Adam to liaise with Simon to check he has background and note that TGM should be involved in review

Noted a media release from Patient Voice Aotearoa had been received This noted several petitions to government and included a petition to continue to fund the Lamictal brand of lamotrigine.

[*Subsequent update on enquiries not discussed at meeting During July 15 enquiries were received by PHARMAC (phone/enquiry email) and in August 7 have been received to date. Key questions were the price of Lamictal and remaining on Lamictal (EC pathway). Enquiries are form patients currently on the Lamictal brand (not Arrow-Lamotrigine)*]

5. **Update adverse event reports:**

Noted no new updates on reporting from CARM and that the next meeting with Medsafe was scheduled for 13 September where investigations and new reports would be discussed.

6 **Lamotrigine data update:**

Noted new data had not been made available. Adam to follow up with analysts. Noted it would be useful to append the updated data to each minute of this meeting

7 **bpacnz article update:**

Noted that the article had been finalised and published with additional clarity on managing dose increases and reductions was clarified and when to seek guidance from the treating neurologist or paediatrician. Adam had passed on thanks to the bpac team for development of the article

Noted the article had been distributed to NANZ, Paediatric Society, League Against Epilepsy and RANZCP asking that it be shared with members

Noted [redacted] was the President of the New Zealand branch of NANZ and it would be useful to send this to her also (Adam to action)

[*Subsequent update not discussed at meeting: in addition has been distributed to the Neurological Subcommittee and Epilepsy New Zealand for distribution to it's educators.* [redacted] *had already received the article*]

8 **Other Business**

Welcomed Hannah to the group who will be taking over as a comms contact on Vikki's departure.

Pete noted in discussions with GP colleagues he has discussed the lamotrigine brand change and no clinical concerns were raised.

Adam noted that he had presented to NZNO Mental Health Nurses section regarding the brand change and no clinical concerns were raised.

Adam noted that CME conferences may be a good mechanism to raise awareness of materials to support the brand change Noted the PSNZ conference was held 10-11 August so this opportunity had been missed for this group. Continue to identify potential opportunities

Adam will circulate the latest data to the group when this is available

9 **Action Items**

1. Vikki to follow up on mechanism for publishing outcome of exceptional circumstances applications
2. Laura and Vikki to follow up with [redacted] re media query
3. Adam to liaise with Simon to check he has background regarding the correspondence to CAC and note that TGM should be involved in review
4. Adam to follow up with analysts for latest data
5. Adam to distribute bpac article to [redacted] ANZAN for dissemination
6. Next meeting Monday 9 September 2019
7. Medsafe meeting Friday 13 September 2019.

Proposal for a double blind, double dummy, cross-over, randomised controlled trial comparing the standard version of an anti-epilepsy drug with a generic version.

I would like to propose that Pharmac fund a double dummy, blinded, cross-over, randomised controlled trial comparing the standard version of an anti-epilepsy drug with a generic version.

I am specifically proposing that Lamictal is compared with the generic brand of lamotrigine, Logem. The same approach could perhaps be used to study other anti-epilepsy drugs, but there would be important ethical issues to consider. (See below)

The problem

Different manufacturers produce different anti-epilepsy drugs (AEDs) that contain the same active agent. Pharmacokinetic studies can be done which show that the drugs are, in theory, comparable However, many patients, pharmacists and doctors are sceptical There is a major risk that the nocebo effect will come into play. Patients report side effects because they do not believe the new product is as good as the original one In addition, because seizures occur in an unpredictable manner, it is likely that some patients who have had their seizures controlled previously, will, at some time, have breakthrough seizures. I see this reasonably often, even when patients remain on the same brand of a drug However, if this happens after a patient changes from one preparation of a drug to another one, the patients usually draw the conclusion that they had the seizure because they changed the drug It is almost impossible to convince an individual patient that this is not the case

The solution

I think the solution is to conduct a double dummy, blinded, cross-over randomised controlled trial comparing the standard version of an anti-epilepsy drug with the generic version.

This would answer the question definitively, and determine if there is a significant difference between the two products Personally, I doubt that there will be, and I think this would answer those who doubt that the generic version is as good as the branded version. I think it could be a really valuable study internationally.

The details would depend on what patient group is being studied The simplest design would be to study patients who are already taking the standard preparation of an AED - in this situation, Lamictal, and who are stable This would include patients who are seizure free, but might include others who have reasonably predictable seizures (i e they have seizures occurring with a certain regularity, such as one or two per month.)

If this was the group being included, then I would propose that the study would go for a year. Patients would all get 6 months of treatment with the Lamictal brand and 6 months of the generic brand. They would also take a placebo of the alternative preparation. Patients would be randomly assigned to the generic or Lamictal brand for the first 6/12 The patients

would keep seizure diaries and record side effects. At the end of the year, the code would be broken and it would be easy to see if there is any difference between the two agents.

The EpiNet study group would be able to undertake this study, in conjunction with the Neurological Association of New Zealand. The EpiNet study group has been set up to conduct clinical effectiveness studies in epilepsy. We are concerned that there is relatively little evidence to guide clinicians when deciding what anti-seizure drugs to use

We are currently undertaking some comparative effectiveness studies of first line anti-seizure drugs in patients with newly diagnosed epilepsy; these are the EpiNet-First trials, in which patients with newly diagnosed epilepsy are randomised to lamotrigine, carbamazepine, levetiracetam or valproate, depending on the seizure type (and whether or not they are women of child-bearing age) These trials are pragmatic, unblinded, randomised controlled trials. (www.epinet.co.nz)

The EpiNet platform would be able to be used to conduct a trial of this nature, though it would require some modification.

Issues to consider

There are a number of issues that would need to be considered.

- Could placebo copies of the different products be obtained? They would need to be identical to the active drugs, and packaged similarly.
- Would the patient's usual pharmacist provide the drugs and placebos, or would patients need to go to a central agency (e.g. a hospital pharmacy?)
- Who would be unblinded? I think it is essential that the patients and physicians are blinded. If patients are to receive their drugs from their usual pharmacy, would the pharmacist be unblinded and dispense the drugs themselves, or would they remain blinded, and simply dispense Product A and Product B?
- Could doctors change the dose of the study drug? I think they would need to be able to do this Presumably, the dose of both the active agent and the placebo would be increased together.
- Would patients need to be on monotherapy? This would certainly make the study easier to perform, though it might restrict the numbers who get recruited. I would suggest that patients do have to be on stable monotherapy when recruited Changing the AED or going onto polytherapy would be one of the secondary end-points of the study.
- Could doctors change the study drug itself? Could another drug be added to the regimen? Again, I think these options would need to be available to the physicians, if the patient either develops intolerable side effects or the study drug is deemed to have failed.
- Should serum levels of the drugs be measured? If so, at what intervals? Would the information be made available to the treating doctors?
- What would the end-points of the study be? I would propose that the primary end-point would be a comparison between the number of seizures experienced by the patients during each phase of the study. Secondary end points would include:
    - The time to the first seizure

- The frequency of side effects
- The severity of side effects
- The number of changes in drug doses
- Whether patients remained on the study drug

The number of patients to be included would be determined by the group being studied. If only patients who had been seizure-free for at least a year were included, then I think the study would probably need to continue for at least one year, and a larger number of patients would probably need to be included. If patients were having, on average, a seizure every week, then the study could be of a much shorter duration (e g 3 months on each product), and fewer patients may be needed. However, it may also be the case that fewer patients would be available to be recruited.

Further Issues re trial-design

Due to the slow titration that is required when starting someone on lamotrigine, I do not think it would be possible to use this design for patients who are starting lamotrigine as a new AED It would still be possible to compare different groups who received either brand of the drug, but they would not be acting as their own controls, since the dosing regimen would clearly be very different in the second period of the study compared to the first period.

This issue would not arise for drugs that do not need to be titrated, though even here, it might take some time to know whether an effective dose of a drug has been reached

Ethical Issues

I think the approach I have outlined here could be used to study any combination of original drug and generic drug However, there would be important ethical issues to consider

The major benefit of comparing Lamictal with Logem is that patients are going to have to change to Logem by October if the study does not proceed. However, if another drug was to be considered (such as sodium valproate) then the question would be: Why would patients want to participate? Particularly, if patients are seizure-free, would there be any reason to take part in a study of this design? If they have not had a seizure for more than a year, they would be entitled to drive If they participated in this study, and did have a seizure, they would lose their ability to drive, and this could have serious repercussions (such as maintaining employment.) I would therefore not recommend to patients on sodium valproate that they should participate in a study of this nature if they were seizure-free and driving. Patients who are not seizure free might still be willing to participate, and they are unlikely to be harmed However, they would be participating for the greater good, and would not be getting anything from the study themselves I think recruitment would therefore be difficult.

[redacted]

Deirdre McCullough

From: [redacted] (ADHB) <[redacted]>
Sent: Wednesday, 19 June 2019 3:19 PM
To: Adam McRae
Cc: [redacted] Home
Subject: FW: Pharmac and Case control study of LTG
Attachments: EQUIGENChronicFinal2016.pdf; Proposal re double dummy RCT.docx

Hi Adam
Here is the document I have prepared re the proposed crossover trial comparing a generic version of an anti seizure drug with the original brand.
I sent it to a statistician (Yannan Jiang) who I have worked with on another trial to get her response Her reply is in the e mail trail below.

I would be interested in knowing if Pharmac are interested in pursuing this any further

I am not sure if you are going to the ENZ Staff conference on Friday, but I am afraid that I will not be there

Best wishes
[redacted]

From: [redacted] [[redacted]]
Sent: Monday, 17 June 2019 11:48 a.m.
To: [redacted] (ADHB)
Subject: RE: Pharmac and Case control study of LTG

HI [redacted],

How are you? It is great to know that the SUDEP NZ study will start soon!

Thanks for the following information and reference (attached). The paper is very interesting, although it is complex in design and analysis which is not surprising for US trials I agree with you that such a trial is possible and important if Pharmac is interested and happy to fund the research.

Depending on the clinical questions relevant to the NZ patient population, the trial design may change accordingly and therefore the sample size. Cross-over trials will require less number of patients than a standard parallel trial design, with a longer study period for the patients completing all treatments in randomly allocated sequences The key assumption is that, there is no carry over effect from the previous drug when patients switch to the next drug treatment and their conditions remain stable as baseline prior to each treatment The equivalence trial is different from non-inferiority or superiority trial, which is not often conducted in NZ. However if you have enough funding for patient recruitment, double-dummy drug preparation and dispensing, and data collections, such a trial will be novel I am happy to help with further discussion and trial design if Pharmac has specific anti seizure drug and patient population of interest.

Thanks,
[redacted]

From: [redacted] <[redacted]>
Sent: Saturday, 15 June 2019 5:09 PM
To: [redacted] <[redacted]>; [redacted] <[redacted]>
Cc: [redacted] <[redacted]>
Subject: RE: Pharmac and Case control study of LTG

Hi [redacted]
I see that a similar study of 35 patients was published in 2016

Michael D Privitera, Timothy E Welty, Barry E Gidal, Francisco J Diaz, Ron Krebill, Jerzy P Szaflarski, Barbara A Dworetzky, John R Pollard, Edmund J Elder, Wenlei Jiang, Xiaohui Jiang, Michel Berg. **Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial**. *The Lancet Neurology*, 2016

Cheers
[redacted]

From: [redacted]
Sent: Saturday, 15 June 2019 5:01 p.m.
To: [redacted]
Cc: [redacted]
Subject: Pharmac and Case control study of LTG

Hi [redacted]
I hope you are well With luck, we will soon be starting our SUDEP study in New Zealand I am attending the discussion of the study by the HDAC Northern A committee on Tuesday.

This e mail, though, is to seek your opinion regarding a quite different study.

You have probably been aware of adverse publicity that arose recently regarding the decision by Pharmac to only fund a single brand of lamotrigine for people with epilepsy.
I proposed to Pharmac that they fund a double blind, double dummy, cross-over randomised controlled trial comparing the Lamictal brand with the generic brand (Logem).
The initial response I had was that the decision regarding lamotrigine has already been made, and Pharmac are unlikely to fund such a study. However, Pharmac would be interested in looking at a proposal to undertake this type of study for other anti-seizure drugs.

Adam Macrae at Pharmac asked me to prepare a short document outlining how such a study would look.

Would you be willing to give me your opinion regarding the attached document?

Do you think a trial such as I propose would be able to demonstrate similar efficacy between the 2 products? Would we need to do a formal non-inferiority study? I have stated that the primary end-point would be a comparison between the number of seizures experienced by the patients during each phase of the study I am aware that this is not really a primary end-point. What should the primary end-point be?
Do we state a null hypothesis that there will be a difference, and set out to disprove this
How do we determine how many patients would need to be recruited?

Do you have any other comments?
Would you be interested in helping with such a study, if Pharmac are interested?

Kindest regards
[redacted]

From: [redacted]
Sent: Monday, 27 May 2019 10:28 p.m.
To: [redacted] (ADHB)
Subject: enquiry@pharmac.govt.nz

Dear Sarah
Would Pharmac consider funding a randomised controlled trial of Lamictal vs the generic brand of lamotrigine (Logem) that is going to be funded from October?

I am the chairman of the EpiNet study group, which has been set up to conduct clinical effectiveness studies in epilepsy We are concerned that there is relatively little evidence to guide clinicians when deciding what anti seizure drugs to use.

We are currently undertaking some comparative effectiveness studies of first line anti-seizure drugs in patients with newly diagnosed epilepsy; these are the EpiNet-First trials, in which patients with newly diagnosed epilepsy are randomised to lamotrigine, carbamazepine, levetiracetam or valproate, depending on the seizure type (and whether or not they are women of child bearing age.) These trials are pragmatic, unblinded, randomised controlled trials (www epinet co nz)

What I am proposing is that we could conduct a double dummy, blinded, cross-over randomised controlled trial

The study would go for a year. Patients would all get 6/12 of treatment with the Lamictal brand and 6/12 of the generic brand. They would also take a placebo of the alternative preparation. Patients would be randomly assigned to the generic or Lamictal brand for the first 6/12. We would get the patients to keep seizure diaries and record side effects, and see at the end of the year if there is any difference between the two agents

This would answer the question definitively and determine if there is a difference between the two products Personally, I doubt that there will be, and I think this would answer those who doubt that the generic version is as good as the branded version. I think it could be a really valuable study internationally.

Clearly, we would need someone to produce placebo versions of the two products (Lamictal and Logem.) I am not sure if the two pharmaceutical companies involved would be prepared to do this

Are you interested in discussing this any further?
Could I give you or one of your colleagues in Pharmac a ring?

Alternatively, someone might like to ring me [redacted] or reply to this e mail

FYI, I am also president of Epilepsy New Zealand, and I oversee the epilepsy surgery programme at Auckland hospital. I did serve a term on the Neurological Subcommittee of Pharmac in the past, but resigned after one term so that I could focus on EpiNet

Yours sincerely
[redacted]

Managing lamotrigine calls.

Key messages:

- Provide reassurance that Logem has the same active ingredient as the other brands of lamotrigine and is delivered to your body the same way.
- Logem should work the same way for you as your old brand of lamotrigine.
- Logem has been approved by Medsafe, the New Zealand Medicines Authority who decides what medicines are safe to use.

If the patient is enquiring about staying on the Lamictal brand:

- The supplier has indicated that they will continue to supply Lamictal in New Zealand. You can talk to your pharmacist to check availability and price.
- PHARMAC will also consider a funding application from a prescriber for a specific brand of lamotrigine for their patients who, due to exceptional clinical difficulties, are unable to manage a change of brand to the sole funded brand or who have not tolerated the change. You will need to discuss this with your doctor as they will have to make this application.

If the patient has experienced an adverse event:

- If a patient is reporting a **serious adverse event*** encourage them to contact their doctor as soon as possible and report to CARM. If appropriate pass the call to the Therapeutic Group Manager (Adrienne or Andrew Oliver) or if not available begin gathering information to compete the lamotrigine contingency check list, file in Objective and notify the TGM. (*a serious event would be considered a sentinel event or one causing patient harm attributed to the brand change which is not expected (e.g. loss of seizure control while driving, injury, or death) if in doubt treat as a serious event)
- If the patient is reporting and adverse event that is not serious encourage them to talk to their doctor and report the event to CARM.
- PHARMAC will also consider a funding application from a prescriber for a specific brand of lamotrigine for their patients who, due to exceptional clinical difficulties, are unable to manage a change of brand to the sole funded brand or who have not tolerated the change. You will need to discuss this with your doctor as they will have to make this application.

Additional reference materials

The Lamotrigine Contingency Plan contains key messages.
A FAQ document has been prepared which has answers it a broader range of common questions.

Lamotrigine brand change contingency plan

From 1 October 2019, Logem will be the sole subsidised brand of lamotrigine. Currently there are three funded brands of lamotrigine, Arrow-Lamotrigine, Lamictal and Logem. Patients currently on Arrow-Lamotrigine or Lamictal will need to transition to the Logem brand.

The purpose of this paper is to provide a contingency plan for any issues that may occur over the transition period. The first part of this paper reiterates key messages that are being communicated assuming no issues arise, while the second part of the paper outlines the Contingency Plan that will be activated if required.

Communication Objective

To keep patients, health professionals and other interested parties reassured, informed and resourced during the brand change via key communication channels.

Communication key messages

What changes are happening?

- The funded brand of lamotrigine is changing from Lamictal, Arrow-Lamotrigine and Logem to Logem only.
- Lamotrigine is a medicine used to treat epilepsy and some mental health conditions, including bipolar disorder.
- From 1 May 2019 to 1 October 2019 people have five months to change to the Logem brand of funded lamotrigine. We are encouraging people to discuss this change with their healthcare professionals early.
- From 1 October 2019 PHARMAC will only fund the Logem brand of lamotrigine. This means that up to 11,000 people will need to change their brand of lamotrigine if they want to continue taking a funded brand of this medicine.
- From 1 October 2019 people will be able to collect a 3-month supply of lamotrigine (Logem brand only) from their community pharmacy.

About Logem and supporting the change

- Logem works in the same way as Lamictal and Arrow-Lamotrigine. Logem has the same active ingredient as the other brands and is delivered to the body in the same way. This means it will have the same effect as the other brands.
- We know change can be difficult for some people. It's understandable that people might have questions about changing brands, but they shouldn't notice any difference when changing to Logem. If people have any questions or concerns about changing their brand of lamotrigine, we encourage them to talk with their healthcare professionals.
- Our dispensing data for 2018 shows that around 50% of all patients who collected a funded prescription for lamotrigine, have changed brands at least once since they started on lamotrigine. Around 4,000 patients have changed brands two or more times. We are not aware of, nor have we been informed of, any significant clinical impacts for these people when they changed brands. Moving to a single funded brand of lamotrigine will avoid ongoing, potentially unmanaged, brand changes for patients.

- The chronic nature of epilepsy means that people, even on treatment, can have recurrent and spontaneous seizures. Expert advice based on a review of literature indicates that just over 1 in 5 people with epilepsy who are stable and have been seizure-free may experience a seizure within 2 years. In general, this is managed through medication review with a patient's doctor and by considering dosage adjustments or a change of medication. We engaged with epilepsy support groups and health professionals before we made the decision to fund one brand of lamotrigine. We have used their feedback to help develop support materials for people changing brands of lamotrigine.
- To help prescribers and pharmacists to support patients changing brands, we have developed a range of resources including patient information, access to 'Beyond the Brand' learning module about brand changes and up to date information about the lamotrigine brand change on the PHARMAC website.
- Some people may return to their GP with concerns following the change to the Logem brand and may need additional support to make a successful change. In these cases, the GP visit co-payment may be waived and PHARMAC will reimburse the GP clinic on invoice. PHARMAC will also consider a funding application from a prescriber for a specific brand of lamotrigine for their patients who, due to exceptional clinical difficulties, are unable to manage a change of brand to the sole funded brand or who have not tolerated the change.

Why have these changes been made?

- PHARMAC's job is to make sure New Zealanders have funded access to the medicines they need. Making brand changes to medicines helps us achieve that by freeing up our fixed budget to fund other medicines in the community.
- Changing which brand of lamotrigine we fund means we'll free up more than $30 million over the next five years, money that PHARMAC will use to fund other medicines for New Zealanders.
- Before deciding to change the funding arrangements for this medicine we got expert advice from healthcare professionals who work directly with people with epilepsy and mental health conditions to make sure it's appropriate for people to change brands of lamotrigine. If our expert clinical advisors said it wasn't appropriate, we wouldn't make the change, regardless of the savings we could achieve.
- If you want more information about what this brand change means for you, please visit our website www.pharmac.govt.nz/lamotrigine or contact us at enquiry@pharmac.govt.nz or 0800 660 050.

Lamotrigine - Contingency planning (Internal document)

The Implementation Lead would be responsible for utilising and actioning the responses identified in this plan as needed. They would be guided by a lamotrigine implementation project team consisting of the relevant TGM, NPPA Team Leader, Communications Advisor and Deputy Medical Director. The Implementation Lead would manage dissemination of regular information to the lamotrigine implementation project team. Information monitored would include Exceptional Circumstances applications received by the NPPA team as well as enquiries from health professionals and reports to CARM.

Potential risks and mitigations during the transition phase (and beyond) of this brand change were identified by the implementation project team. The attached table details the risks, the actions and communication messages associated to support the mitigation of each risk.

The main risks that have been identified are as follows:

1. Reports of breakthrough seizures, mood destabilisation or adverse effects in one or more patients
2. Reports of serious or sentinel events causing patient harm
3. Adverse and/or sustained reporting via media or social media
4. Withdrawal of Arrow-Lamotrigine from New Zealand by Teva
5. Withdrawal of 2mg and/or 5mg presentations of Lamictal by GSK
6. Out of stocks by supplier of Logem Mylan

The level of risk and associated likelihood have been indicated in the attached table.

If any of the risks identified occur, PHARMAC staff involved in the project will immediately alert the Senior Leadership Team (SLT), the Clinical Risk and Outcomes Committee (CROC) and Communications team as per the plan.

The objectives of this contingency plan are to:

- Keep patients and health professionals reassured, informed and resourced during the transition phase of this brand change.
- Keep key sector partners reassured and informed during the transition phase including Medsafe, CARM, MoH and the Minister of Health.
- Implement the planned contingency and communication activities as outlined in the table attached if any of the risk scenarios happen.
- Respond appropriately to any adverse events to ensure patient safety.
- Manage any adverse publicity which may arise from any of the scenarios
- Ensure staff are informed if any of these risks are triggered and that messaging is consistent throughout the organisation.

- Ensure all identified risks are mitigated and monitor the progress of the brand change activities.

	Risk Scenario	Health Professionals actions	PHARMAC's response/role	Timeframe/outcomes	Communication plan and responsibilities	Reports generated
1.	**Reports of break through seizures, mood destabilisation or adverse effects in one or more patients being attributed to the brand change** **Impact:** MEDIUM **Likelihood:** HIGH	Prescriber identifies the patient is experiencing break through seizures, increase in seizure frequency, mood destabilisation or adverse effects indicating excess or reduced lamotrigine levels Patient to be managed by their treating clinician as per usual practice, may consider checking adherence, levels and/or dose adjustment Contact PHARMAC to inform issues occurring. Report to CARM if an adverse event is identified.	**TGM** to review reported issues (including those reported to PHARMAC identified via Exceptional Circumstances applications, CARM reporting and PHARMAC enquires 0800 line or email) as they are notified and liaise with the lamotrigine implementation project team and Director of Operations as necessary to appropriate identify approaches Notify and discuss with Medical Director or Deputy Medical Directors and NPPA Team Leader as necessary If management measures are not sufficient to improve clinical outcomes consider escalating to risk scenario two below as appropriate and complete check list	Undertake assessment within a week	Key messages: • Logem works in the same way as Lamictal and Arrow Lamotrigine Logem has the same active ingredient as the other brands and is delivered to the body in the same way. This means it will have the same effect as the other brands • The chronic nature of epilepsy means that people, even on treatment, can have recurrent and spontaneous seizures. Expert advice based on a review of literature indicates that just over 1 in 5 people with epilepsy who are stable and have been seizure free may experience a seizure within 2 years. In general, this is managed through medication review with a patients GP and by considering dosage adjustments or a change of medication. • PHARMAC is aware of the issue and is liaising with the treating clinician(s) We are monitoring the outcome • The clinical teams are managing this with their patients and PHARMAC is supporting them with information and expert advice. Key spokespeople: Director of Operations Medical Director or Deputy Medical Director	**TGM** to report to Manager Pharmaceutical Funding weekly, copied to the Medical Director as necessary **Implementation Lead** to send a fortnightly update sent to lamotrigine implementation project team. **Implementation Lead** to send an email update to the (CROC) **Implementation Lead** to liaise with Communications Team to provide no surprises update to Minister monthly/as required
2.	**Reports of serious sentinel event causing patient harm being attributed to the brand change** **Impact:**	Prescriber believes the patient is experiencing serious adverse effects causing patient harm or has experienced a sentinel event (e g loss of	**PHARMAC staff** receiving notification to refer to TGM or complete a check list for follow up. This relates to reports received directly by PHARMAC	Patient will be managed by the treating clinician and be in regular contact with them (in hospital or outpatient).	Key messages: • PHARMAC is working closely with the clinicians and our expert advisors to	**Implementation Lead/TGM** to inform lamotrigine implementation project team, CROC and SLT

	Risk Scenario	Health Professionals actions	PHARMAC's response/role	Timeframe/outcomes	Communication plan and responsibilities	Reports generated
	HIGH **Likelihood:** **LOW**	seizure control while driving, injury, or death) that is possibly related to the brand change Contact PHARMAC to notify as soon as possible Encourage reporting of the adverse event to CARM if this has not been done.	stff (i.e. not 3rd party reports e.g. CARM). PHARMAC staff likely to include enquires team, NPPA team and TGM. **Implementation Lead** to coordinate development of checklist in conjunction with TGM, lamotrigine implementation project team and Medical (see the checklist). See Objective folder to capture completed checklists **Implementation Lead** to establish regular meetings with Medsafe to review CARM adverse event reports **TGM** to review completed checklist. Discuss with Manager Pharmaceutical Funding/Medical Director/ lamotrigine implementation project team. Determine input required from the NPPA panel examining lamotrigine Exceptional Circumstances funding. Consider if advice is required from expert member of Mental Health or Neurological Subcommittees or NPPA Advisory Panel. Assess the following: • Clinical risk to patient and whole patient group • Should patient remain on Logem or change back to their previous brand of lamotrigine? (if appropriate) • Communication with other relevant specialists to raise awareness of the sentinel event and recommended action points (TGM to action, Medical Director to send)	PHARMAC assessment and decisions on next steps complete within maximum 48 hours. If this is a more widespread issue, a full communications plan to be initiated	understand the particular events surrounding this case • We will communicate any further information as soon as we are able • There is a specific process for considering funding in exceptional circumstances for individual patients who, due to exceptional clinical difficulties, are unable to manage a change of brand • Details on how to apply for exceptional circumstances funding are available on our website • The chronic nature of epilepsy means that people, even on treatment, can have recurrent and spontaneous seizures Expert advice based on a review of literature indicates that just over 1 in 5 people with epilepsy who are stable and have been seizure-free may experience a seizure within 2 years. In general, this is managed through medication review with a patients GP and by considering dosage adjustments or a change of medication Spokespeople: Director of Operations Medical Director or Deputy Medical Director Communications team: Manager Communications and Communications Adviser to be alerted All communications to be reviewed and approved between Operations; E&I; Medical teams	**Implementation Lead** to liaise with Communications Team to report to Minister as necessary (to be determined on case by case basis) **Medical Director** to email nominated contact and relevant clinical groups with feedback on issues to all relevant specialists if appropriate (not with patient specific detail)

	Risk Scenario	Health Professionals actions	PHARMAC's response/role	Timeframe/outcomes	Communication plan and responsibilities	Reports generated
3.	**Adverse and/or sustained reporting via media or social media** **Impact:** MEDIUM **Likelihood:** HIGH		**Communications Adviser** to undertake regular monitoring of media and social media and report any messages about the brand change are to the lamotrigine implementation project team Respond to media enquiries and assess requirement to respond to social media posts/messages in a timely manner	Fortnightly reporting with responses as required	Key messages (depends on what is said via what channel) where possible these should reflect the key messages contained in the first section of this document Spokespeople: Director of Operations Medical Director	Reactive approach **Communications Adviser** and **Implementation Lead** to co-ordinate with relevant parties to on responses **Communications Adviser** to monitor impact of PHARMAC response via social media channel or in mainstream media **Implementation Lead** to provide summary of media activity to lamotrigine implementation project team to assess and consider the need for a reactive media strategy based on the frequency and reach of media
4.	**Withdrawal of the Arrow Lamotrigine brand from supply in New Zealand by Teva post 1 October 2019** **Impact:** MEDIUM **Likelihood:** HIGH		**TGM/Procurement Manager** to liaise with treating clinicians and pharmacy to procure Arrow-Lamotrigine stock from overseas for patients funded to use that brand via EC/NPPA Contact wholesalers if needed. **NPPA Funding Coordinator** to communicate to individual applicants and treating clinician informing of stock issues and how to obtain supply (if known) Costs involved in sourcing Section 29 stock would be covered via the Exceptional Circumstances framework For successful Expectational Circumstances consider if Lamictal brand would be a suitable alternative	Monitor throughout transition and ongoing if Exceptional Circumstances application approved for Arrow Lamotrigine	Key messages: • We are aware of this stock situation and are doing everything we can about it • We are working with specialists and pharmacies to ensure patients who rely on this medication will not be affected with this stock issue. Additional messages if necessary: • PHARMAC does not have a contract with the supplier of Arrow-Lamotrigine Spokesperson: Director of Operations	Stock issues reported from wholesalers, pharmacies or hospitals ad hoc **Contract Manager/TGM** to report to Manager Pharmaceutical Funding, Manager P&C and & DoO as necessary **Implementation Lead** to provide update to lamotrigine implementation project team and CROC **Implementation Lead** to liaise with comms to provide a no surprises update to Minister as necessary

	Risk Scenario	Health Professionals actions	PHARMAC's response/role	Timeframe/outcomes	Communication plan and responsibilities	Reports generated
5.	**Withdrawal/supply issues with 2mg and/or 5mg presentations** **Impact:** MEDIUM **Likelihood:** LOW	Pharmacies to inform PHARMAC if having problems securing supplies of 2mg and 5mg lamotrigine dispersible tablets	**Contract Manager/TGM** to liaise with wholesalers and pharmacies to procure 2mg and 5mg lamotrigine dispersible tablets Assess costs involved in sourcing section 29 stock, provide financial support to pharmacies as necessary to avoid costs being passed onto patients	Ongoing monitoring	Key messages: • We are aware of this stock situation and are doing everything we can about it • We are working with pharmacies and GSK, the supplier of Lamictal, to ensure patients who rely on this medication will not be affected by this stock issue Additional messages for DHBs/funders if necessary: • PHARMAC does not have a contract with the supplier of Arrow-Lamotrigine • There is an indemnity clause in the contract with the manufacturer, of Lamictal (GSK) which means the supplier will pay any additional costs for a failure to supply Spokesperson: Director of Operations	Stock issues reported from wholesalers, pharmacies or hospitals ad hoc **Contract Manager/TGM** to report to Manager Pharmaceutical Funding, Manager P&C and & DoO as necessary **Implementation Lead** to provide update to lamotrigine implementation project team and CROC **Implementation Lead** to liaise with comms to provide a no surprises update to Minister as necessary
6.	**Out of stocks by supplier of Logem Mylan** **Impact:** HIGH **Likelihood:** LOW	Pharmacies to inform PHARMAC if having problems securing supplies of Logem	**Contract Manager** to receive updates on stock levels from Mylan and review progress with brand change in relation to stock levels weekly **TGM** to implement dispensing restrictions if required If stock shortage does occur, communication to prescribers and pharmacies with information of stock issues and strategies put in place to ensure supply for patients already on Logem	Ongoing in event of identifying supply issues	Key messages: • We are aware of this stock issue and are working with the supplier • We understand there haven't been any patients affected by this stock issue • We will continue to closely monitor the shortage with the supplier Additional messages for DHBs/funders: • There is an indemnity clause in the contract with the manufacturer, which means the supplier will pay any additional costs	**Contract Manager** to provide weekly sales and stock levels from manufacturer (Contract manager/TGM to review) **Contract Manager/TGM** to report to Manager Pharmaceutical Funding, Manager P&C and & DoO as necessary **Implementation Lead** to provide update to lamotrigine implementation project team and CROC **Implementation Lead** to liaise with comms to provide a no surprises update to Minister as necessary

	Risk Scenario	Health Professionals actions	PHARMAC's response/role	Timeframe/outcomes	Communication plan and responsibilities	Reports generated
					Spokesperson: Director of Operations	

PHARMAC
Pharmaceutical Management Agency

NEUROLOGICAL AND MENTAL HEALTH SUBCOMMITTEE MEMORANDUM

From: Therapeutic Group Manager

Date: January 2019

Matters arising: Proposal to switch to one funded brand of lamotrigine

QUESTIONS TO SUBCOMMITTEE

Questions relevant to both epilepsy and mental health conditions

1 What is the Subcommittees' view on the information provided by Medsafe, in particular with regards to the literature cited in Medsafe's letters?

2. What is the Subcommittees' view on the updated literature review provided by PHARMAC staff?
3. What is the Subcommittees' view on the consultation responses?
4. What is the Subcommittees' view on the implementation activities suggested by Medsafe?
5. Do the Subcommittees agree with Medsafe's description of who 'the most vulnerable patients' are (those who are seizure free and those with labile seizures)?
    a Are there any other patient groups the Subcommittees consider to be equally vulnerable?
6. Should GPs refer the 'most vulnerable patients' for specialist oversight of a brand switch?
    a. If yes to above, how many patients would this likely be?
    b. What would be the specialist oversight that would be provided?
    c How many clinic visits would these patients require?
7. What is the likely clinical situation of patients who take both venlafaxine and lamotrigine?
    a Given the difficulties that some patients experienced with the recent venlafaxine switch would the Subcommittees have increased concerns about switching this subset of patients?

8 Do the Subcommittees consider that there needs to be an alternative funding mechanism available for patients who are either unable to switch brands or need to switch back to their original brand?
    a How many patients would likely apply?
    b. What criteria could we use to assess any applications for those who are unable to switch brands or need to switch back to their original brand?
    c. What information should be provided, and by whom?

d. If PHARMAC was to create a Panel of clinicians to assess applications, what scope of practice should be represented on the Panel (e.g. Neurologists and Psychiatrists)?

9. Are the Subcommittees still comfortable with PHARMAC progressing with a move to one funded brand of lamotrigine, supported by the implementation activities noted in this paper and an exceptions mechanism?
10. Do the Subcommittees consider that a longer transition (i.e. longer than the previously advised 3-6 months) would be needed to support a brand change should the proposal go ahead?
11. Do the Subcommittees have any comments/suggestions regarding the proposed implementation activities noted in this paper?
12. CARM reports and hospital admissions are currently the only mechanisms we can access to monitor breakthrough disease. Are the Subcommittees' aware of any other mechanisms we could use to access this information?
    a. If no to above, are the Subcommittees aware of how we would find this information?

Questions relevant to epilepsy

13. What is the Subcommittees' view of the updated UK Medicines & Healthcare products Regulatory Agency (MHRA) advice about switching between different manufacturers' brands of anti-epileptic drugs (AEDs)?
    a Based on this updated information does the (Neurological) Subcommittee wish to change any of its previous considerations relating to AEDs and MHRA categorisation?
14 With regards to the MHRA's advice on category 2 AEDs; what do the Subcommittees' consider the role of the primary care team (e.g. GP, practice nurse) could be in supporting a patient with epilepsy through a brand change of lamotrigine?
    b Is the MHRA advice specific to those who are taking AEDs for epilepsy?
    c. What services would be required from the primary care team in supporting a lamotrigine brand change?
    d Could these services be provided by a supporting clinical role other than the GP (e.g. practice nurse or nurse practitioner)?
    e. Would this be necessary for all patients taking lamotrigine for epilepsy or just a subset of these?
        i. If only necessary for a subset, how could the group be clinically defined?
15 What symptoms, that may indicate a risk of reduced/increased bioavailability with lamotrigine, should HCPs be reminded of?
    f. Specifically, for people with epilepsy?
16 Is there any information regarding employment and/or driving a vehicle that people with epilepsy and their prescribers need to discuss prior to changing brands of lamotrigine?

Questions relevant to mental health conditions

17. What mental health conditions, apart from bi polar affective disorder, is lamotrigine prescribed for?
18. What does the Subcommittee consider the role of the primary care team (eg GP, Practice nurse) could be in supporting a patient with a mental health condition through a brand change of lamotrigine?
    a What services would be required from the primary care team in supporting a lamotrigine brand change?
    b Could these services be provided by a supporting clinical role other than the GP (e.g. practice nurse or nurse practitioner)?
    c. Would this be necessary for all patients taking lamotrigine for a mental health indication or just a subset of these?
        i. If only necessary for a subset, how could the group be clinically defined?
19 What symptoms, that may indicate a risk of reduced/increased bioavailability with lamotrigine, should HCPs be reminded of?
    a. Specifically, for people with a mental health condition?
20 What information regarding employment and/or driving a vehicle would people with a mental health condition and their prescribers need to discuss prior to changing brands of lamotrigine?

PURPOSE OF THIS PAPER

The purpose of this paper is to seek clinical advice on concerns that were raised during consultation on a proposal to move to one funded brand of lamotrigine (Logem); and, to seek clinical advice on possible implementation activities to support the change (should it go ahead)

DISCUSSION

BACKGROUND

PHARMAC currently funds three brands of lamotrigine: Lamictal, Logem and Arrow-Lamotrigine, at a total annual net cost of [redacted]

There are approximately 12,500 patients taking lamotrigine; 62% of which are on Lamictal brand, 26% Arrow-lamotrigine brand and 12% Logem brand Based on our analysis ~58% of patients are taking lamotrigine for a mental health indication; and ~42% for epilepsy Approximately 50% have of all patients who last received a prescription for lamotrigine in 2018 have switched brands at least once (52% of epilepsy patients and 46% of mental health patients). More details on page 12-16.

The opportunity for significant savings coupled with the need to meet budget and fund new investments led us to run a Request for Proposals (RFP) (*a commercial process*) for sole supply of lamotrigine This was informed by advice/support from both Neurological and Mental Health Subcommittees. The RFP was run in June 2018 and a preferred proposal was selected, for sole supply of Logem

In August 2018, PHARMAC issued a consultation on a proposal to move to one funded brand of lamotrigine (Logem)

- The effect of the proposal would mean that all people taking any other funded brand of lamotrigine 25mg, 50mg and 100 mg dispersible tablets (Lamictal, supplied by GSK; and Arrow-Lamotrigine, supplied by Teva) would have 5 months to transition to the Logem brand This would be approximately 11,000 people (89% of all lamotrigine patients) changing brands (data regarding patient numbers is presented on page 15).

- Should the proposal go ahead it would mean significant savings of approximately $32 million over 5 years (NPV) (please note this is confidential) This is a substantial amount of savings that PHARMAC could use to fund other pharmaceuticals.

A number of concerns, related to both epilepsy and mental health, were raised during consultation. After reviewing all of the feedback, we determined that we require additional time to consider the issues raised before a decision can be made on the proposal. We communicated this update publicly in October 2018.

Medsafe provided the most substantive feedback and we have since discussed its concerns with them in detail Following this engagement we determined that we needed to seek additional clinical advice from both the Neurological Subcommittee and Mental Health Subcommittees We note the outcome of this transaction will likely affect how we approach other similar transactions in the AED area and given the sums of money involved, and opportunities for significant savings for reinvestment, we are taking the feedback extremely seriously and are committed to finding the best outcome to enable the savings to be realised while ensuring that patients continue to have good health outcomes from lamotrigine

Clinical advice related to lamotrigine and other AED brand switches

Neurological Subcommittee advice

In November 2015, the Neurological Subcommittee provided clinical advice on antiepileptic (AED) brand switching

In summary, with regards to lamotrigine, the Neurological Subcommittee considered:

- that a managed switch to one brand of lamotrigine would be preferable to having multiple brands listed and that a competitive process for one brand of lamotrigine would be appropriate Full details of the minutes are available in appendix 1

With regards to the MHRA categorisation (based on the MHRA 2013 advice) for AEDs the SC provided the following advice:

- The Subcommittee considered the MHRA categorisation to be pragmatic and was broadly supportive of the majority of the categorisation, with two exceptions. The Subcommittee was unable to come to a consensus in relation to lamotrigine; whether it should be in category one or two, or in category two or three
- The Subcommittee considered that AEDs in category one have a narrow therapeutic index and should only have one brand listed to avoid inadvertent brand switching. The Subcommittee noted that there is only one brand of carbamazepine, phenytoin, phenobarbital (phenobarbitone) and primidone (category one of the MHRA guidance) listed in the Pharmaceutical Schedule.

- With regards to category two of the MHRA categorisation (including lacosamide), the Subcommittee expressed a preference for a managed brand switch if, as a result of a competitive process, a sole supply arrangement was entered into which resulted in one brand of AED being funded The Subcommittee considered that a managed brand switch would require a transition period of 3 to 6 months.
- The Subcommittee considered that switching between brands for AEDs in category three (not including lacosamide) was unlikely to be clinically problematic. The Subcommittee noted that levetiracetam tablets (category three of the MHRA guidance) had previously changed brands and that the transition of this had been acceptable.

Full details of the minutes are available in Appendix 1

Mental Health Subcommittee advice

In November 2016, the Mental Health Subcommittee provided clinical advice on lamotrigine brand switching. In summary, the Subcommittee considered that it would not be clinically problematic from a mental health standpoint to switch patients from one brand of lamotrigine to another if necessary (that is, no more or less problematic than any other mood stabiliser brand change) Full details of the minutes are available in Appendix 2

Consultation responses summary

PHARMAC received 32 responses to the August 2018 consultation on a proposed brand switch for lamotrigine Eight of the responses were from Health Care Professionals (HCPs), 17 from consumers, 3 from Suppliers and 4 from others. Responders included clinicians and HCPs, lamotrigine suppliers, the Royal Australian and NZ College of Psychiatrists (RNZCP), the NZ League Against Epilepsy (NZLAE), the Pharmacy Guild, consumer organisations (Epilepsy NZ, Epilepsy Waikato), government organisations (Medsafe, NZTA), consumers and an academic.

Themes raised by responder type, are summarised in the table below (table 1). The individual consultation responses are attached in Appendix 3

In summary, HCPs were generally supportive of the proposal. Concerns regarding the potential for loss of seizure control or mood destabilisation were raised by consumers, consumer groups and pharmaceutical suppliers. The most substantive response we received was from Medsafe and relates to clinical advice provided by the Neurological Subcommittee For this reason, a summary of the concerns raised by Medsafe is provided in a separate paragraph below table 1.

Table 1: Consultation feedback

Responder type	Themes and summary of feedback
Clinicians, HCPs	Supportive One Neurologist noted that bioequivalence is likely to be close between the different manufacturers. Any differences in bioequivalence will be less than the rather large steps (usually 25mg) that dose adjustments are made by clinicians Savings can be applied elsewhere in the health system

	One Neurologist provided a reference in support of AED brand switching (Holtkamp & Theodore. Epilepsia. 2018;59:1273 81.) (Reference attached in Appendix 7) Highlighted the importance of maintaining supply of the 2 mg and 5 mg tablets Possibility for reduced workload due to one brand Harm unlikely due to pharmaceutical or pharmacokinetic variation but may arise due to poor patient medicine management. A change will require clinician and support services time to prevent this One responder noted that they previously switched 30 patients to Logem and only one out of 30 changed back due to taste. One responder highlighted concerns around some GSK marketing material that is misleading.
NZLAE	Supportive. Consider the change needs to be managed well at a pharmacy level. Patients need to be informed that the change will not impact their seizure control Highlighted the importance of maintaining supply of the 2 mg and 5 mg tablets Highlighted importance of continuity of supply. Consider that all epilepsy patients should be given 3 months supply of their medication at once
RANZCP	Supportive, provided patients are supported during the transition. Suggests careful messaging to assist people changing to the new formulation Considers that in some rare situations the Logem brand may not have the same subjective efficacy and may not be well tolerated by some consumers or even result in relapse in some individuals. Therefore, would support a process where individuals may seek alternative treatment options.
Academic [redacted]	Supportive. Considers that there is clear evidence that changing brands does not lead to adverse health outcomes, citing a publication (of which she is a co-author) Lessing et al Appl Health Econ Health Policy 2014;12:537 46 (Reference attached in Appendix 7)
Pharmacy Guild (membership organisation for pharmacy owners)	Considers that people with epilepsy and bipolar disorder are generally averse to change and that previous brand changes for these groups have been challenging. Concerns about loss of seizure control from a brand change Considers that research shows that brand changes can have flow on effects resulting in increased healthcare costs from hospitalisations and ED admissions (Kjoenniksen et al. Pharm World Sci. 2006;28:284 9.) (Reference attached in Appendix 7)
New Zealand Transport Association (NZTA)	No concern Change in brand and not a treatment change. While there are some minor differences in pharmacokinetics between brands, these particular ones are not mainstream medications for epilepsy, and any risk from changing would be extremely low

Lamotrigine Suppliers (GSK – Lamictal supplier and Teva, Arrow-lamotrigine supplier)	Not supportive Consider that there is a risk of loss of seizure control when switching brands of AEDs. Widespread brand switching of AEDs is not recommended by the majority of international bodies One supplier (GSK) provided references to support its submission. References related to lamotrigine and brand switching have been included in Appendix 7. For a full list of the references that GSK included please see its response, included in Appendix 3 One supplier highlighted the recent brand change for venlafaxine and expressed its views on how the transition had gone (noting that it was an unsuccessful bidder to the venlafaxine RFP).
Consumer groups (Epilepsy NZ + Epilepsy Waikato)	Not supportive Concerns about loss of seizure control. Noted the impacts that loss of seizure control can have: loss of licence, loss of employment, mental health issues, burden on health system (Dr visits, hospital admissions, injury), loss of independence, effects on education and learning, effects on family/relationships and death (SUDEP or accident eg drowning). Expressed a lack of confidence for brand changes based on recent venlafaxine change Considered that any savings from this proposal should be reinvested into the health of people with epilepsy. There needs to be an alternative pathway for those who need to switch back to their old brand
Consumers	Not supportive. Highlighted concerns about potential for loss of seizure control or side effects. Noted loss of seizure control can have implications for the following: ability to drive, cognitive function, career, increased hospital/Dr visits, financial burden, loss of accommodation, effects on family/relationships, level of independence/confidence, mental health and emotional wellbeing. Considered that there should be an alternative mechanism to consider people who are not able to change brands Considered that there is a lack of information and support provided by pharmacists when changing brands. Concerned that HCPs may not be aware of the change (if it happens) Concerned about the potential for re occurrence of currently well managed bipolar symptoms, Concerned about the potential for increased health care needs such as admission to acute Mental Health facilities, respite care, or increased need for support from Community Mental Health Concerned that the Neurological Subcommittee did not reach a consensus about what MHRA category lamotrigine should be in.

	Highlighted concerns about a lack of information and support during the venlafaxine brand change. One responder cited three relevant articles ((Crawford et al. Seizure. 2006;15:165-76), (LeLorier et al Curr Med Res Opin 2008;24:1069 81), (Wick, J Y (2014). Switching Antiepileptic Drugs: Benefits Versus Risks)). Attached in appendix 7. Concerns for people who take both venlafaxine and lamotrigine as they have just been through a brand change for venlafaxine and some experienced anxiety and depression as a result. Concerns for changing brands while pregnant. Considered that we will be removing patient choice.

Medsafe consultation feedback

The Medsafe consultation response (letter dated 19 September 2018) (attached in Appendix 4) highlighted concerns about switching brands of antiepileptic medicines and about the evidence that was considered by the Neurological Subcommittee in support of this. The response also cited references, and updated advice from the MHRA, not previously considered by the Subcommittee.

PHARMAC staff met with representatives from Medsafe (on 13 November 2018) to better understand the issues raised in Medsafe's feedback. In summary, we understood the following from this meeting (full details are available in the file note, Appendix 4):

- Medsafe considers that lamotrigine should be considered a Category 2 anti-epileptic medicine in relation to the MHRA advice for brand switching/prescribing, noting this advice was updated in late 2017.
- Lamotrigine is not a narrow therapeutic index medicine
- All generic brands of lamotrigine approved in New Zealand are all considered bioequivalent to the innovator, Lamictal
- With the exception of one recent (unpublished) article regarding anti epileptic brand switching, and the articles provided in Medsafe's consultation feedback, Medsafe was not aware of other important studies of interest that had not been considered by the Neurological Subcommittee.

However, following this meeting we received an additional response from Medsafe to clarify its position regarding potential funding changes for lamotrigine. This letter (dated 21 November 2018) highlighted additional concerns with the literature considered by the Subcommittee and a suggestion that a review of the scientific literature may reveal additional useful information. It also provided some suggestions for implementation should the proposal go ahead:

- All patients should be reviewed by their GP before switching brands, and counselling should be provided by a GP before the patient gets to their pharmacy (before the patient has their prescription dispensed).
- GPs should refer the most vulnerable patients (those who are seizure free and those with labile seizures) for specialist oversight of a brand switch.
- A patient leaflet, to help explain the changes, should be provided by GPs, specialists and pharmacists.

- All patients should be actively followed up to check they are coping with the change.
- An alternative funding mechanism should be made more accessible for patients who need to switch back to their original brand.

We subsequently wrote back to Medsafe (email dated 18 December 2018), to clarify several points that were raised in the letter (21 November 2018) and also to thank them for their feedback and let them know that we would be seeking further advice from our clinical advisors (email attached in Appendix 4).

We have attached all cited references from Medsafe in appendix 6 and have summarised the various studies in table 7 (on page 23). The updated MHRA (Medicines and Healthcare products Regulatory Agency, United Kingdom) advice referred to by Medsafe is available on page 7 from this link We have also conducted a review of the scientific literature which is discussed in further detail below.

MHRA categorisation

In 2013 the MHRA issued advice about switching between different manufacturer's AEDs, and subsequently update it in 2017 The 2013 advice was considered by the Neurological Subcommittee at its 2015 meeting.

A summary of the MHRA's 2013 and 2017 advice regarding the categorisation of AEDs is provided below. Full details are available from here.

MHRA categorisation of AEDs (Table 2)

Category	2013 MHRA advice	2017 MHRA advice
Category 1 Carbamazepine, Phenobarbital, Phenytoin, Primidone	Doctors are advised to ensure their patient is maintained on a specific manufacturer's product.	For these drugs, there are clear indications that clinically relevant differences between different manufacturers' products might occur, even when the pharmaceutical forms are the same and bioequivalence has been shown Ensure that the patient is maintained on a specific manufacturer's product.
Category 2 Clobazam, Clonazepam, Eslicarbazepine, Lamotrigine, Oxcarbazepine, Perampanel, Retigabine, Rufinamide, Topiramate, Valproate, Zonisamide	Need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with patient and/or carer taking into account factors such as seizure frequency and treatment history	Drugs that do not fit into Category 1 or 3 Base the need for continued supply of a particular manufacturer's product on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency and treatment history Take into account patient/carer-related factors such as their negative perceptions about alternative products and/or other issues related to the patient should also be taken into account
Category 3 Brivaracetam, Ethosuximide, Gabapentin,	It is usually unnecessary to ensure that patients are maintained on a specific manufacturer's product unless there are specific	These drugs show all the following characteristics: High solubility across the relevant range of pHs; Essentially complete absorption after oral administration; Dose-

Lacosamide, Levetiracetam, Pregabalin, Tiagabine, Vigabatrin	concerns such as patient anxiety and risk of confusion or doing errors	response curves for efficacy and safety are not steep; Therapeutic Index is not narrow. For these drugs, the potential for clinically relevant differences to exist between different manufacturers' products is considered to be extremely low. However, consider other patient/carer-related factors, such as negative perceptions about alternative products and/or other issues related to the patient.

In addition to this the MHRA, in 2017, provided the following advice for healthcare professionals

- Core advice from 2013 remains in effect for prescribing AEDs to manage epilepsy.
- Consult the 3 categories of antiepileptic drugs when deciding whether it is necessary to maintain continuity of supply of a specific manufacturer's product.
- As well as the classification, when evaluating whether continuity of supply should be maintained for category 2 or 3 drugs, consider:
    - Perception by patients of differences in supply, for example differences in product presentations
    - Co-morbid autism, mental health issues, or learning disability.
- If you think a patient should be maintained on a specific manufacturer's product, prescribe either by specifying brand name or by using the generic drug name and name of the manufacturer

Implementation plans (should the proposal go ahead)

PHARMAC has gained extensive experience in managing difficult or complex brand switches, including the recent diabetes management products, venlafaxine brand switches and haemophilia treatment brand changes While we acknowledge that a lamotrigine brand change could be challenging for people taking lamotrigine, should the proposed change proceed, there are a range of activities PHARMAC could implement to address the challenges and support a successful transition. As well as the usual PHARMAC processes and information to support decisions (such as notification letter and emails to key stakeholder groups, Pharmaceutical Schedule updates, and PHARMAC website update), some extra activities could include:

Lamotrigine specific options:

- PHARMAC to cover the patient's appointment fee for General Practitioners or Practice Nurses who would likely be required to spend time to support people at the primary care level who are changing their brand of lamotrigine. MHRA advice suggests that HCP oversight is required for people with epilepsy, and that suggestion has prompted this potential implementation activity.
- Develop patient specific information about the change to be used by HCPs when supporting patients with the change this could be accessible on the PHARMAC

website and hard-copies printed. An example of a leaflet used for the venlafaxine brand change is included in Appendix 9

- Ensure regular face to face meetings with Medsafe, CARM and PHARMAC as required before and during the brand change transition period and for the first 12 months of sole supply to ensure consistent messaging and health sector approach.
- Provide information on the PHARMAC website about the brand change for prescribers, other health care professionals, community pharmacy and consumers. Include access to a range of resources (in multiple languages if considered appropriate) explaining the change for consumers. Ensure the website is updated regularly about the change in response to the questions raised by stakeholders through PHARMAC enquiries
- Develop a video, hosted on our website to explain the brand change to consumers.
- Request development of a written resource for HCPs in primary care by BPACnz to support the transaction and lamotrigine brand change for the month the new funded brand of lamotrigine is listed on the Pharmaceutical Schedule. The resource would include what practitioners are required to do when counselling the change in brand.
- Support Epilepsy New Zealand Field officers who work with people in the community who are living with epilepsy This could include supporting training on generics and brand switches. The training sessions could be facilitated by and presented by specialists and primary care providers.
- Depending on the advice we receive from the Subcommittees one option we are open to exploring would be to create an alternative funding mechanism (e g utilising a Panel of clinicians to assess applications) for patients to remain/return to a particular brand of lamotrigine We received feedback from consultation that a dedicated mechanism for this may be more appropriate than our usual mechanism for considering exceptional circumstances (NPPA) More details about alternative funding mechanisms and the role a Panel would have is provided below on page 12

Broader options

- Implement a series of nationwide presentations for healthcare professionals about generics and generic brand switches and consider using lamotrigine as one of the examples presented Attendance could be eligible for CME points This could be implemented through the current 'PHARMAC seminar' approach, or a separate, stand-alone series
- Consider utilising the lamotrigine brand change as an opportunity to get real world experience on whether counselling on the nocebo effect alters the acceptance of a brand change, using lamotrigine as the pharmaceutical for this research. This could be done in conjunction with researchers at the Department of Psychological Medicine, Auckland University, who are interested in this area of research.
- Publish consumer stories on the PHARMAC website, where a person receiving a funded generic medicine talks about their successful change from one brand to another Lamotrigine could be one of the change examples

We are interested in feedback from Subcommittee members about the necessity, suitability and potential context required in these proposed activities should the brand change proceed.

PHARMAC's exceptional circumstances framework

PHARMAC's role includes considering whether to fund pharmaceutical treatments for people in exceptional circumstances when those treatments are not currently available for them on the Pharmaceutical Schedule The Exceptional Circumstances Framework outlines the ways in which PHARMAC generally considers funding decisions for exceptional circumstances that fall outside of the Pharmaceutical Schedule funding process, and guides PHARMAC's decision making in these cases. The Framework includes the Named Patient Pharmaceutical Assessment (NPPA) Policy and other processes through which PHARMAC considers exceptional circumstances. Details regarding PHARMACs exceptional circumstances framework is available here.

As noted earlier in this paper, depending on the advice of the Subcommittees' PHARMAC are open to exploring the use of an alternative funding mechanism to help support a lamotrigine brand switch.

Another example, in addition to NPPA, of PHARMAC's use of the exceptional circumstances framework is the alternative funding mechanism that was established to consider applications for specific brands of haemophilia treatments.

- In 2015 PHARMAC ran an RFP for haemophilia treatments that resulted in a large number of patients having to switch brands of their haemophilia treatment. Further details are available here PHARMAC established an expert panel (the Haemophilia Treatments Panel) to consider applications for funded access to alternative funded brands of haemophilia treatments
- The Haemophilia Treatments Panel is largely comprised of haematologists who treat haemophilia Clinicians are required to make an application to the Haemophilia Treatments Panel for funded access to their patients original brand if they consider a switch to the new funded brand could compromise appropriate clinical care for their patients.
- General guidance as to what might be considered clinically appropriate reasons to avoid switching a patient has been provided to clinicians. This guidance was informed by advice we received from the Haemophilia Subcommittee Further details about the Panel are available here

For the Subcommittees information Panels typically comprise a group of clinicians determining, on PHARMAC's behalf, whether certain clinical criteria are met. Panels evaluate applications against specified criteria and they apply their collective clinical expertise to this task. Panels are particularly useful when it is difficult to set firm access criteria often the case in areas where accurate diagnosis or evaluation of benefit is particularly complex Panels also help to reduce inter-applicant variability, something that is particularly important in niche areas.

Lamotrigine dispensing data

As noted earlier in the paper there are currently three funded brands of lamotrigine listed (Lamictal, Arrow Lamotrigine and Logem). As there are multiple brands listed, switching can

occur at a pharmacy level unless the prescription has been annotated with the brand and it is specified on the prescription that no brand substitution is allowed

The dispensing data in table 3 below provides a breakdown on:

- the number of patients we have estimated to be taking lamotrigine for either epilepsy or other indications (likely mood disorders); and
- the proportion patients on each brand of lamotrigine; and
- the proportion of patients who have switched brands at least once for each of the identified groups (epilepsy and other indications).

The data in table 4 provides a further breakdown to show the numbers of patients who have switched multiple times

On a separate but related note we are aware from consultation feedback that there may be some patients who are taking both venlafaxine and lamotrigine concurrently We have sourced dispensing data (see table 5) to help estimate how many people this may apply to; noting that people taking venlafaxine have recently switched brands so this information may be useful to help inform our implementation plans. We seek the Subcommittees' advice on what the clinical situation of these patients is likely to be; and, given the difficulties that some patients experienced with the recent venlafaxine switch would the Subcomittees' have increased concerns about switching this subset of patients

Literature Search

Evidence Previously Considered by PHARMAC

As noted above, in November 2015, the Neurological Subcommittee of PTAC provided PHARMAC with clinical advice regarding antiepileptic brand switching (Neurological Subcommittee of PTAC November 2015). At this time, the Subcommittee considered evidence provided by the publications listed in Table 6 below.

Table 6: Summary of evidence previously considered by the Neurological Subcommittee of PTAC (Appendix 5)

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
Chaluvadi et al. Epilepsia 2011;52:810-5.	Retrospective chart review	Epilepsy	n = 260	To describe the outcomes of a compulsory switch from branded to generic levetiracetam	• 43% of patients receiving generic levetiracetam switched back to brand name levetiracetam • Results compared to other studies in which patients were required to switch from branded to generic drugs including lamotrigine (switchback 12.9%) and valproate (switchback 20.9%)	N/A
Erickson et al. Epilepsia 2011;52:1365-71.	Retrospective cohort study	Epilepsy	N = 1490 (n = 745 switch)	To determine if switching from branded to generic AEDs is associated with adverse outcomes	• Lamotrigine brand to generic switching was not associated with utilisation changes (incidence rate ratio 1.00; 95% CI 0,84 to 1.19) or emergency department visits/hospitalisations (event rate ratio 0.97; 95% CI 0.80 to 1.17)	N/A
Gagne et al. Clin Pharmacol Ther 2010;88:347-53.	Case-crossover study	Epilepsy/ seizures	N = 1762	To estimate the risk of seizure-related events associated with refilling prescriptions of AEDs to estimate the effect of	• Refilling the same AED was associated with an elevated risk of seizure-related events whether or not the refill involved switching from a branded to a generic product	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
				switching between brand and generic or two generics	• Switching between brand and generic was associated with a higher event risk than switching between generic products from different manufacturers, but this was based on few cases with overlapping odds ratios	

Hansen et al. Epilepsy Res 2013;106:237-43.	Case-control study using data from a commercial claims database	Epilepsy	N = 9110	To investigate the association between switching brand name and generic AEDs and the odds of emergent treatment for a seizure-related event over a 1-year period	• Modest association between AED switching and seizure-related events
					  ○ Unadjusted odds ratio (OR) of a seizure-related event for switching was 1.38 (95% CI 1.24 to 1.58; *P*<0.0001)
					  ○ Adjusted OR of a seizure-related event for switching was 1.27 (95% CI 1.14 to 1.41)
					• The risk of an event increased with number of comorbidities
					• Authors concluded that the behaviour of switching may lead to seizure-related events regardless of the medication or type of switch; healthcare professionals should be cautious of switching between bioequivalent AEDs
						N/A

Hartung et al. CNS Drugs 2012;26:707-16.	Retrospective cohort-crossover study among patients with sustained	Epilepsy, bipolar disorder, depression, migraine, neuropathic	N = 616	To evaluate potential adverse outcomes of generic substitution of lamotrigine for diverse indications	• Conversion to generic lamotrigine was not associated with a significant increase in ED visits (15.1% conversion period vs 13.0% control period; adjusted odds ratio [AOR] = 1.35; 95% CI 0.92 to 1.97) or hospitalizations (2.9% conversion period vs 2.4% control	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
	Medicaid enrolment	pain, other pain			period; AOR = 1.21; 95% CI 0.60 to 2.50) • The authors noted that type II error could not be ruled out, and that the population included only patients enrolled in Medicaid	
Kesselheim et al. Drugs 2010;70:605-21.	Systematic review and meta-analysis	Epilepsy	N/A	To evaluate studies comparing brand-name and generic AEDs to determine whether there is evidence that brand-name AEDs are superior in maintaining seizure control	• 16 articles were identified: 9 RCTs, 1 prospective non-randomised trial, and 6 observational studies • Overall, the brand-name AEDs were not better or worse than generic versions in maintaining seizure control (aggregate odds ratio [n=204] 1.0; 95% CI 0.7 to 1.4) • The observational studies identified changes in drug or health services utilization that was attributed to less adequate seizure control with generic products	N/A
Kinikar et al. Ann Pharmacother 2012;46:650-8.	Pre-post, self-controlled, retrospective study	History of seizure	N = 222	To compare within-patient seizure control before and after switching from brand to generic phenytoin	• The proportion of patients experiencing confirmed seizure events was not significantly different between pre- and post-switch periods (12.2% vs 11.3%; adjusted *P* = 0.545)	Kaiser Permanente
Lessing et al. Appl Health Econ Health Policy 2014;12:537-46.	Retrospective study using national health and pharmacy claim datasets	Majority epilepsy	N = 1655 (n = 361 switched from	To evaluate the health outcomes of patients switching from	• There were no significant differences in the number of ED visits, hospital admissions, use of specialist services, deaths, or use of other AEDs pre- and	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
	in New Zealand		originator to generic)	originator to generic lamotrigine	post-index date between switchers and non-switchers • Switching from originator lamotrigine to a generic equivalent resulted in no significant differences in health outcomes	
Polard et al. Pharmacoepidemiol Drug Saf 2015;24:1161-9.	Case-crossover study using the French National Health Insurance Database	Epilepsy	n = 8379	To assess the association between brand-to-generic substitution of AEDs and seizure-related hospitalization	• Brand-to-generic AED switch was not associated with an elevated risk of seizure-related hospitalisation (unadjusted OR 0.97; 95% CI 0.86 to 1.10: adjusted OR 0.97; 95% CI 0.85 to 1.10) • No significant interaction was identified in subgroup analyses (gender, age, free or non-free, strict AED monotherapy or not)	N/A
Shin et al. Int J Clin Pharmacol Ther 2014;52:1017-22.	Retrospective study using records from a single tertiary hospital	Epilepsy	N = 80	To determine whether switching from generic to generic phenytoin is associated with change in clinical outcomes	• After switching, 41% of patients experienced increasing seizure events • The number of medical visits for acute seizure activity significantly increased in the post-interchange period • There was a significant difference in bioavailability between generic phenytoin agents	N/A
Talati et al, Pharmacotherapy 2012:32:314-22.	A systematic review	Epilepsy	N/A	To assess the efficacy, tolerability, and safety of innovator versus generic AEDs	• 71 studies included for qualitative analysis, 18 studies included for quantitative analysis • Data limited primarily to carbamazepine, phenytoin, and valproic acid	The Agency for Healthcare Research

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
					• Initiating a generic AED provides similar efficacy, tolerability, and safety to initiating an innovator AED • Evidence from observational studies suggested that switching from one form to another may be associated with an increased risk of hospitalisation and longer hospital stays	and Quality (AHRQ)
Ting et al. Epilepsia 2015;56:1415-24.	Randomized, double-blind, multiple-dose, steady-state bioequivalence study (BEEP)	Epilepsy	N = 34	To investigate whether generic lamotrigine approved via healthy volunteer testing would meet the same bioequivalence standards as brand-name lamotrigine when tested in patients potentially sensitive to switching ("generic-brittle" patients)	• Generic lamotrigine demonstrated bioequivalence to brand-name lamotrigine • Within-subject variability was similar for generic lamotrigine and brand-name lamotrigine • Few subjects had seizure exacerbations or tolerability issues with product switching • The authors concluded that the FDA bioequivalence standards are acceptable in "generic-brittle" patients with epilepsy • "generic-brittle" was defined as having a potential problem with generic switching by virtue of (1) a history of reported prior exacerbation of seizures or side effects following AED formulation changes; (2) intolerable AED side effects within the last year prior to study; or (3) refractory seizures within the last year prior to study, which could reflect clinical sensitivity to slightly higher AED peak	FDA

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
					plasma concentration or slightly lower drug exposure, respectively.	
Vari et al. Clin Drug Investig. 2016;36:87-91.	Prospective, single-arm, multicentre study	Focal or generalized epilepsy	N = 59	To evaluate the safety and tolerability of brand-to-generic levetiracetam switch	• At 6 months following an overnight switch from brand-name to generic levetiracetam, there was no significant difference in seizure frequency or intensity, or occurrence of adverse events • At the end of the study, the switchback rate was 3.4%	N/A
Yamada & Welty. Ann Pharmacother 2011;45:1406-15.	Systematic review	Primarily epilepsy	N/A	To evaluate the efficacy and safety of generic AED substitution and PK analysis	• 20 studies included: 7 retrospective studies, 6 prospective studies in patients with epilepsy, 7 prospective studies in healthy subjects • Retrospective studies showed a significant relationship between generic substitution and increased health care utilization due to seizures or toxicity • Prospective studies showed no differences between brand and generic drugs in PK and bioequivalence; and no significant differences in seizure frequency	N/A

AEDs, antiepileptic drugs; PK, pharmacokinetics; RCTs, randomised controlled trials.

Evidence Provided by Medsafe

A number of articles were provided to PHARMAC by Medsafe during ongoing correspondence regarding the potential lamotrigine brandswitch. These publications are listed in Table 7 below.

Table 7: Summary of evidence provided by Medsafe (Appendix 6)

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
Atif et al. Springerplus. 2016;5:182.	Systematic review	Epilepsy	N/A	To evaluate the risks associated with generic substitution of AEDs	• 68 articles were included • Potential problems identified with substitution of generic lamotrigine included increased breakthrough seizures, toxicity and increased serum lamotrigine levels, and adverse effects	N/A
Berg et al. JAMA Neurology. 2017;74:919-926.	Single-dose, crossover, prospective, sequence-randomised, replicate PK study (EQUIGEN)	Epilepsy	N = 50	To evaluate the single-dose PK bioequivalence of three immediate-release lamotrigine drug products (one branded, two generic)	• The three drug products were bioequivalent in people with epilepsy taking concomitant antiepileptic drugs • No significant differences in within-subject variability were identified between the three products	FDA, Epilepsy Foundation, and the American Epilepsy Society
Desmarais JE et al. CNS Neurosci Ther. 2011;17:750-760.	Literature review	Indications requiring psychotropic medications	N/A	To review the clinical equivalence between generic and original psychotropic medications	• Issues identified in patients receiving generic formulations of lamotrigine included increased seizures, adverse events, toxicity, and healthcare utilisation; need for additional pharmaceuticals; and anticonvulsant hypersensitivity syndrome	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
Kesselheim et al. Drugs 2010;70:605-21. (repeated in Table 1)	Systematic review and meta-analysis	Epilepsy	N/A	To evaluate studies comparing brand-name and generic AEDs to determine whether there is evidence that brand-name AEDs are superior in maintaining seizure control	• 16 articles were identified: 9 RCTs, 1 prospective non-randomised trial, and 6 observational studies • Overall, the brand-name AEDs were not better or worse than generic versions in maintaining seizure control (aggregate odds ratio [n=204] 1.0; 95% CI 0.7 to 1.4) • The observational studies identified changes in drug or health services utilisation that was attributed to less adequate seizure control with generic products	N/A
Lang et al. Ann Neurol. 2018; doi: 10.1002/ana.25353. [Epub ahead of print].	Retrospective analysis of a database valid for the German population	Epilepsy	N = 3530	To investigate the risk of recurrent seizures after switching the manufacturer of the same AEDs	• Patients with seizures had switched drug manufacturers both from branded to generic and between generics more often than controls • Switching the manufacturer was an independent risk-factor for experiencing seizure recurrence • In previously seizure-free patients, switching the manufacturer was associated with a higher risk of seizure recurrence	N/A
Lessing et al. Appl Health Econ Health Policy 2014;12:537-46 (repeated in Table 1)	Retrospective study using national health and pharmacy claim	Majority epilepsy	N = 1655 (n = 361 switched from	To evaluate the health outcomes of patients switching from originator to generic lamotrigine	• There were no significant differences in the number of ED visits, hospital admissions, use of specialist services, deaths, or use of other AEDs pre- and post-index date between switchers and non-switchers	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
	datasets in New Zealand		originator to generic)		• Switching from originator lamotrigine to a generic equivalent resulted in no significant differences in health outcomes • The authors concluded that the results argue against the interchangeability of AEDs of different manufacturers	
Lessing et al. Value Health. 2015;18:646-654.	Retrospective study using data from patients using venlafaxine in New Zealand	Depression	N = 14,232	To investigate the impact on patients switched from originator to generic venlafaxine	• 12% of originator brand users switched to generic venlafaxine • 88% of new originator brand users did not switch • 60% of new users of generic venlafaxine switched to the originator brand • There were too few new users of generic venlafaxine to detect differences between switchers and non-switchers • For existing or new originator brand users there were no significant differences in health service use between switchers and non-switchers	N/A
Liow et al. Neurology. 2007;68:1249-50.	Position statement	Epilepsy	N/A	To outline the American Academy of Neurology's (AANs) principles concerning coverage of anticonvulsants for adults and children with epilepsy	• Variation between name-brand and generic drugs can be highly problematic for patients with epilepsy • The AAN opposes generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician's approval	American Academy of Neurology

AEDs, antiepileptic drugs; PK, pharmacokinetics.

Evidence Provided in Response to Consultation

A number of articles have been provided to PHARMAC during the consultation process regarding lamotrigine brand switching. These publications are listed in Table 8 below.

Table 8: Summary of evidence provided to PHARMAC in response to consultation (Appendix 7)

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
Crawford et al. Seizure. 2006;15:165-76.	Literature review	Epilepsy	N/A	To explore potential problems with generic substitution of AEDs	• 70 relevant articles were identified • A number of potential problems with generic substitution were identified • The limited evidence available supports concerns regarding switching older AEDs	N/A
Holtkamp & Theodore. Epilepsia. 2018;59:1273-81.	Critical review and invited commentary	Epilepsy	N/A	To summarise and evaluate the evidence for bioequivalence, health care utilisation, and safety of generic AEDs	• Clinical studies suggest there is little risk from switching to and among generic AEDs • The authors recommend that generics be prescribed when a new AED is initiated • Switches from brand-to-generic and generic-to-generic are generally safe but should be accompanied by counselling	N/A
Kjoenniksen et al. Pharm World Sci. 2006;28:284-9.	Retrospective review of a pharmacy database	Not specified (patients receiving ≥3 drugs)	N = 386	To assess patients' attitudes towards and experiences of generic switching after three years in Norway	• 36% (n = 50) of patients who had experienced a switch reported one or more negative experiences and 21% (n = 29) reported an overall negative experience • Patients undergoing generic drug substitution may need additional information and support	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
					• Generic drug substitution was not perceived as an equal alternative to branded drugs by all patients	

LeLorier et al. Curr Med Res Opin. 2008;24:1069-81.	Retrospective analysis of medical and pharmacy claims data	Epilepsy	N = 671	To analyse the proportion of patient switching from generic to branded drugs among users of AEDs compared with other areas and healthcare utilisation among these patients	• 27.9% (n = 187) switched from branded to generic lamotrigine; 27.5% (n = 51) switched back to the branded medication
					  ○ Rates of switchback for various AEDs ranged from 20.8% to 44.1%
					  ○ Rates of switchback for non-AEDs ranged from 7.7% to 9.1%
						N/A

Lessing et al. Appl Health Econ Health Policy 2014;12:537-46 (repeated in Table 1 & 2)	Retrospective study using national health and pharmacy claim datasets in New Zealand	Majority epilepsy	N = 1655 (n = 361 switched from originator to generic)	To evaluate the health outcomes of patients switching from originator to generic lamotrigine	• There were no significant differences in the number of ED visits, hospital admissions, use of specialist services, deaths, or use of other AEDs pre- and post-index date between switchers and non-switchers • Switching from originator lamotrigine to a generic equivalent resulted in no significant differences in health outcomes • Relative to branded lamotrigine, generic lamotrigine was associated with increased mean daily dose of lamotrigine, higher number of dispensations of other AEDs and non-AEDs, higher utilization of medical services, and longer hospital length of stay	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
Liow et al. Neurology. 2007;68:1249-50 (repeated in Table 2)	Position statement	Epilepsy	N/A	To outline the American Academy of Neurology's (AANs) principles concerning coverage of anticonvulsants for adults and children with epilepsy	• Variation between name-brand and generic drugs can be highly problematic for patients with epilepsy • The AAN opposes generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician's approval	American Academy of Neurology
Privitera MD. Epilepsy Curr. 2008;8:113-7	Review	Epilepsy	NA	To present the current state of bioequivalence and therapeutic equivalence and to propose studies to better clarify the risks of generic formulation substitution in susceptible populations	• Data from physician surveys, case reports, and switchback studies imply that generic and brand drugs may not be equal for all patient groups • Studies are needed to determine whether the complaints regarding seizures after switching to generic AEDs are due to bio-inequivalence, therapeutic inequivalence, or other factors (e.g. placebo, nocebo, stress, comorbidities, progression of underlying illness) • Until there are adequate studies investigating the risk of switching to generic formulations, patients with epilepsy should proceed cautiously, and extra care may be needed for patients at high risk of seizure complications	N/A
Wick, J.Y. (2014). Switching Antiepileptic Drugs: Benefits Versus Risks.	Opinion/ review	Epilepsy	N/A	Overview of the benefits and risks of switching AEDs	• There continues to be controversy regarding switching AEDs • The benefits and risks of switching must be considered, and vigilance during the switch must be maintained	Pharmacy Times sponsored content

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
					• Switching provides an opportunity to improve seizure control and/or reduce adverse events	

AEDs, antiepileptic drugs.

PHARMAC Literature Search

In January 2019, PHARMAC staff conducted a PubMed search using search terms including lamotrigine, antiepileptic, brand switch, switch, and generic; and also completed an unstructured Google Scholar search in order to identify relevant publications not previously considered or brought to PHARMAC's attention by stakeholders. The relevant publications are included in Table 9 below. Note that some articles are duplicated between searches and are included only once, and that articles already summarized in the tables above are not repeated.

PubMed search results:

- Lamotrigine AND brand switch: 9 results; 9 relevant
- Lamotrigine AND generic: 54 results; 20 relevant
- Lamotrigine AND switch*: 150 results; 16 relevant
- Antiepileptic AND switch* AND generic: 100 results; 35 relevant (please note that preference was given to systematic reviews, articles published since 2015 and articles contained lamotrigine in the title).

Table 9: Summary of evidence identified in a literature search conducted by PHARMAC in January 2019 (Appendix 8)

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor

Andermann et al. Epilepsia. 2007;48:464-9.	Retrospective analysis of public-payer pharmacy-claims database from Ontario	Epilepsy	N = 1354	To quantify switchback rates from generic to brand-name AEDs in comparison with other drugs and to document potential adverse consequences of generic switching, focussing on lamotrigine	• 12.9% of generic lamotrigine users switchback to branded lamotrigine
					  ○ Switchback rates for clobazam and divalproex were ~20%
					  ○ Switchback rates for AEDs were higher than non-AEDs (1.5 to 2.9%)
					• Lamotrigine doses were increased after generic substitution (6.2%; *P*<0.0001)
					• The number of co-dispensed AEDs and non-AEDs increased after generic substitution (11.0% and 15.6%, respectively; both *P*<0.0001)
						GlaxoSmith Kline

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
Bautista et al. Epilepsy Res. 2011;95:158-67.	Survey of adult epilepsy patients	Epilepsy	N = 121	To determine the factors associated with increased seizures and side effects after switching from brand to generic AEDs	• Of the 71 individuals who switched from branded to generic AEDs, 18 (25.7%) reported definite increased seizure frequency • 14 (19.7%) individuals reported increased side effects; the most common were unsteadiness, dizziness, and headaches	N/A
Berg MJ. Neurology. 2007;68:1245-1246.	Editorial	Epilepsy	N/A	Opinion piece regarding the problems associated with generic AEDs	• There is discordance between the FDA's position that all approved generic AEDs are equivalent to the branded equivalent and the majority of physician/patient perception that they are not • If action is wanted, physicians should provide incident data to the FDA using MedWatch	N/A
Boylan LS. Neurology. 2009;72:1876-7.	Commentary	Psychiatric and neurologic indications	N/A	Commentary on LeLorier et al. 2008 (summarized below)	• The study by LeLorier et al. 2008 which investigated the risks associated with patients switching to and from generic AEDs, did not consider that changes could be attributed to promotionally driven physician and patient preference • The suggestion that dose increases were due to increased side effects is counterintuitive; Boylan suggests that anxiety-induced dose escalations contributed to side effects and subsequent switch backs • The data blurred psychiatric and neurological indications for lamotrigine	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
Carbon M & Correll CU. CNS Drugs. 2013;27:353-65.	Literature search	Psycho-tropic agents (various indications)	N/A	To evaluate the degree of bioequivalence and therapeutic equivalence of branded and generic psychotropic drugs	• Not all medications containing the same active pharmacological ingredient have the same biological activity; whether these differences are clinically important will depend on the needs of each patient • For lamotrigine – three retrospective studies are reviewed: two reported a switch to generic resulted in higher doses of lamotrigine and increased medical resource utilization, and one reported increased adverse events measured in ED visits, hospitalization, and changes in co-prescription	N/A
Contin et al. Epilepsy Res. 2016;122:79-83.	Retrospective analysis of prospectively collected data from a therapeutic drug monitoring database	Epilepsy	n = 250	To assess intrasubject variation in plasma concentrations of lamotrigine, levetiracetam, and topiramate after generic substitution compared with a stable brand name drug regimen	• The proportion of patients showing an intrasubject change greater than ±20% in lamotrigine plasma concentration was 22% in the brand-to-generic switch group compared with 33% in the stable brand name group • The rate of AED-related adverse events was similar between groups • The authors concluded that significant day-to-day variability in intra-patient plasma lamotrigine can be observed even in patients stabilized on brand-name products	N/A
Erickson et al. Epilepsia. 2011;52:1365-71.	Retrospective cohort study using a health insurance plan claims database	Epilepsy	n = 1990	To determine if switching from branded to generic AEDs is associated	• No difference in AED utilization changes was reported for patients switching to generic lamotrigine vs non-switch patients (incidence rate ratio 1.00; 95% CI 0.84 to 1.19)	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
				with adverse outcomes	• No difference in adverse events as measured by all-cause ED visits and hospitalizations was reported for patients switching to generic lamotrigine vs non-switch patients (event rate ratio 0.97; 95% CI 0.80 to 1.16) • Authors noted that the findings suggested that lamotrigine may be switched from brand to generic formulation without increased ED visits or hospitalizations or changes to therapy	
Holtkamp M. Nat Rev Neurol. 2019;15:8-9.	Commentary	Epilepsy	N/A	Commentary on Lang et al. 2018 (summarized in Table 2 above)	• Lang et al. 2018 demonstrated that switching between AEDs from different manufacturers increased the risk of seizure relapse • Holtkamp notes that while the assumption is that seizure worsening can be attributed to a pharmacological issue, wider evidence suggests that poor treatment adherence might be responsible • Evidence suggests that concerns regarding the broad range of bioequivalence accepted by regulatory bodies may be overestimated • In Lang et al. 2018, the cause of seizure relapse after switching could not be analysed – Holtkamp notes that no increase in seizure activity was observed when switching from generic to brand suggesting that the cause may not be pharmacological; Holtkamp suggests the cause may be non-adherence	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
					• Holtkamp concludes that switching between AEDs should be safe provided basic recommendations are followed (e.g., no unnecessary switching, patient counselling, check AED serum concentrations)	
Kesselheim et al. JAMA Intern Med. 2013;173:202-8.	Case-control study of commercially insured patients in the US	Epilepsy	N = 11,472	To determine whether switching among different appearing AEDs is associated with medication non-persistence	• Colour discordance preceded 1.2% of cases of non-persistence and 0.97% controls (adjusted OR 1.27; 95% CI 1.04 to 1.55) • Shape discordance preceded 0.16% of cases of non-persistence compared with 0.11% of controls (OR 1.47; 95% CI 0.85 to 2.4) • Changes in pill colour but not shape increased the risk of non-persistence among the subgroup of patients with a seizure disorder diagnosis within 6 months prior to the index date (colour: OR 1.53, 95% CI 1.07 to 2.18; shape: OR 3.15; 95% CI 0.82 to 12.1)	N/A
Kesselheim et al. Neurology. 2016;87:1796-1801.	Population-based case-crossover study using Medicaid and UC commercial health insurance database	Epilepsy, myoclonus, convulsions	N = 83,001	To determine whether refilling generic AEDs and switching between different manufacturers were associated with increased seizure incidence and whether refilling or pill appearance changes might	• Generic AED refilling was associated with an 8% increase in the odds of a seizure-related event (OR 1.08; 95% CI 1.06 to 1.11) • The odds of a seizure related event increased following a switch to a different manufacturer (OR 1.09; 95% CI 1.03 to 1.15); however, after adjustment for refilling, there was no association (OR 1.00; 95% CI 0.94 to 1.07)	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
				modify any association		
Krauss GL. JAMA Neurol. 2017;74:900-901.	Editorial	Epilepsy	N/A	Opinion regarding the three FDA-funded bioequivalence studies	• The FDA-funded studies were only conducted using lamotrigine, and therefore may not be relevant to all AEDs • The FDA-funded studies did not include disparate generic formulations of lamotrigine • The FDA-funded studies inform on bioequivalence, but do not address common patient complaints and clinical problems with generic switching • Discussing the FDA-funded studies with patients may reduce 'nocebo' effect	N/A
Kwan P & Palmini A. Epilepsy Behav. 2017;73:166-172.	Systematic review	Epilepsy	N/A	To review changes in healthcare utilization following AED switch	• 14 retrospective articles included • The three studies that investigated a brand-to-generic lamotrigine switch reported that there was no increased risk of acute events (ambulance use, ER visits, hospitalization); one of these studies reported an increased risk of outpatient visits and hospitalization duration, but not inpatient visits • Pooled AED switch studies were inconsistent with five reporting increased healthcare utilization and five reporting no increase in healthcare utilization	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
Labiner et al. Neurology. 2010;74:1566-74.	Retrospective open-cohort study using a US health insurance claims database	Epilepsy	N = 33,625	To investigate the association of generic AED use with all-cause and epilepsy-related medical resource utilization and injury risk	• Drugs included were carbamazepine, gabapentin, phenytoin, primidone, or zonisamide (lamotrigine not included) • Compared with brand use, generic AED use was associated with greater medical utilization and risk of epilepsy-related medical events	N/A
Lalic et al. Drugs R D. 2011;11:53-60.	Clinical PK study	Epilepsy	N = 16	To investigate the variation in lamotrigine serum concentrations between two immediate-release tablet formulations	• There were no significant differences in lamotrigine serum concentrations between the two formulations	Ministry of Science and Technology, Republic of Serbia
Liow et al. Neurology 2007;68:1249-1250.	American Academy of Neurology (AAN) position statement on anticonvulsants	Epilepsy	N/A	Position statement on the use of anticonvulsant drugs for the treatment of epilepsy	• The AAN opposes generic substitution of anti-convulsant drugs for the treatment of epilepsy without the attending physician's approval • Anticonvulsant drugs differ from other classes of drugs; small variations in concentration can cause toxic effects and/or seizures • The AAN opposes policies that would result in arbitrary switching among anticonvulsants • The AAN supports legislation that would require informed consent of physicians and patients before generic substitutions are made at the point of sale	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
					• The AAN believes that the use of anticonvulsants for epilepsy should be distinguished from use for other indications	
Makus KG & McCormick J. Clin Ther. 2007;29:334-41.	Case series analysis (survey)	Epilepsy	71 pharmacist responses and 130 physician responses	To characterize outcomes in patients with epilepsy who experienced adverse reactions on switching from branded to generic lamotrigine and who were subsequently switched back to branded lamotrigine	• The survey responses indicated that ≥80% of patients who experienced a loss of seizure control when switching from brand to generic lamotrigine regained seizure control when switched back to branded lamotrigine	GlaxoSmith Kline
Miller JE et al. Neurology. 2007;69:1806-8.	Response to Position Statement (Liow et al. 2007 above)	Epilepsy	N/A	Response to Position Statement (Liow et al. 2007 above)	• The consideration of restricting generic prescriptions of AEDs is surprising as there is scant hard evidence of problems with current generic AED formulations • Prospective, blinded, randomized trials are required to address whether generic AEDs achieve different serum levels than branded versions • Barriers to generic competition are not in the patient's interest	N/A
Nielsen et al. Epilepsy Behav. 2008;13:127-30.	Pilot PK analysis	Epilepsy	N = 9	To report on comparative PK data obtained with different	• Despite narrower bioequivalence requirements in Denmark, there are some patients who experience serious clinical consequences (seizure relapse, status	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
				preparations of lamotrigine in outpatients reporting problems with shifts in lamotrigine preparation	epilepticus, epidural hematoma due to ataxia and falls) in association with a change in lamotrigine preparation and significant alterations in plasma levels	
Patel et al. Epilepsy Res. 2012;98:269-72.	Short communication	Epilepsy	N = 18	To report on patients taking stable lamotrigine who were found to have significant increases in serum LTG concentrations	• Mean serum lamotrigine concentrations had increased significantly over time despite no change in treatment regimen • GlaxoSmithKline confirmed that lamotrigine in the later time period was sourced from a different site • The authors concluded that lamotrigine levels can fluctuate resulting in toxicity even if a stable regimen of the parent compound is being used	N/A
Privitera M. Neurol Clin Pract. 2013;3:161-164.	Clinical practice opinion	Epilepsy	N/A	Overview of the controversial area of generic substitution of AEDs	• Controversy remains regarding the 'switchability' between brand and generic AEDs • Critique of bioequivalence testing include that testing is not conducted on people with epilepsy, that the test population is not taking other medications, that studies investigate a single dose, and that outcomes or adverse effects are not considered • Studies suggesting that seizure control and adverse effects may change after generic substitution are primarily retrospective • The FDA has funded three ongoing prospective studies to address questions	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
					regarding AEDs beyond standard FDA bioequivalence analysis	
Privitera et al. Lancet Neurol. 2016;15:365-72.	Randomised, double-blind, chronic dosing, crossover, PK study (EQUIGEN)	Epilepsy	N = 35	To study the effect of switching between two disparate generic lamotrigine products in patients with epilepsy	• Lamotrigine exposures were equivalent between the generic products (bioequivalence in C_{max} and AUC) • No significant differences in seizure frequency or adverse events were reported	FDA, the Epilepsy Foundation, the American Epilepsy Society
Rahman et al. Epilepsy Res. 2017;135:71-78.	Retrospective analyses of the FDA Adverse Event Reporting System (FAERS)	Epilepsy	N/A	To compare adverse event reporting rates for brand vs generic AEDs including lamotrigine	• 27,150 events were reported for lamotrigine: 71% for branded, 27% for generics, and 1.64% for authorized generics • The reporting odds ratio (ROR) for branded lamotrigine was higher for severe dermatologic events and diplopia; the ROR for generic lamotrigine was higher for suicide/suicidal ideation and dementia compared with branded and authorised generic	FDA
Rascati et al. Pharmacotherapy. 2009;29:769-74.	Case-control analysis	Epilepsy	N = 3964	To determine the odds of AED substitution among patients who had an epileptic even requiring acute care relative to patients with no event	• 11.0% of patients who had an acute event had an AED substitution in the 6 months prior compared with 6.3% of controls (patients with no event) • The authors concluded that patients who had an epileptic event requiring acute care were ~80% more likely than matched controls to have had a recent AED substitution	N/A

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
Vossler et al. Epilepsy Curr. 2016;16:209-211.	American Epilepsy Society (AES) position statement on generic substitution of AEDs	Epilepsy	N/A	To update the 2007 position statement in the light of two FDA-funded bioequivalence studies	• The results of the two FDA-funded bioequivalence studies of lamotrigine support the validity of the FDA's bioequivalence standards • Patients and providers can now have reasonable confidence of bioequivalence when switching from brand-to-generic or generic-to-generic AEDs	N/A
Wilner AN. Epilepsy Behav. 2004;5:995-8.	13-question survey for neurologists	Epilepsy	n = 301	To assess the effects of generic substitution of AEDs	• 68% of neurologists reported breakthrough seizures after a switch from brand-to-generic AEDs (33% for generic-to-generic) • 56% of neurologists reported increase side effects after a switch from brand to generic AEDs (27% for generic-to-generic) • 18% of neurologists agreed that the FDA standards for AED bioavailability are sufficiently narrow. • The authors concluded that although switching may be appropriate for some patients, there are a substantial number for whom generic substitution may represent suboptimal care	Shire, Inc., US
Zachry et al. Epilepsia. 2009;50:493-500.	Case-control analysis	Epilepsy	N = 1664	To evaluate the association between inpatient/ emergency epilepsy care and the occurrence of a recent switch in AED formulation	• 11% of case patients experienced a switching between AED alternatives within 6 months compared with 6.5% of the control patients (OR 1.81; 95% CI 1.25 to 2.63; *P* = 0.0024) • Cases requiring acute care therefore had 81% greater odds of having undergone an	Abbot Laboratories

Citation	Study Design	Indication	Patient no.	Objective	Key Messages	Sponsor
					AED formulation switch within the previous 6 months than matched controls	

AEDs, antiepileptic drugs; PK, pharmacokinetics.

THE FACTORS FOR CONSIDERATION

Factors are presented here in the order they appear in the paper, without implying any ranking or relative importance.

NEED

- The health need of the person
- The availability and suitability of existing medicines, medical devices and treatments
- The health need of family, whānau, and wider society
- The impact on the Māori health areas of focus and Māori health outcomes
- The impact on the health outcomes of population groups experiencing health disparities
- The impact on Government health priorities

HEALTH BENEFITS

- The health benefit to the person
- The health benefit to family, whānau and wider society
- Consequences for the health system

SUITABILITY

- The features of the medicine or medical device that impact on use by the person
- The features of the medicine or medical device that impact on use by family, whānau and wider society
- The features of the medicine or medical device that impact on use by the health workforce

COSTS AND SAVINGS

- Health-related costs and savings to the person
- Health related costs and savings to the family, whānau and wider society
- Costs and savings to pharmaceutical expenditure
- Costs and savings to the rest of the health system

PHARMAC
TE PĀTAKA WHAIORANGA

Level 9, 40 Mercer Street, Wellington
PO Box 10254, Wellington 6143, New Zealand
P: +64 4 460 4990 | F: +64 4 460 4995
www.pharmac.govt.nz

29 July 2019

Louise Upston MP
Via email upston.cambridge@parliament.govt.nz

Dear Louise

Lamotrigine funding

Thank you for your email about your constituent with epilepsy who is concerned about the lamotrigine brand change.

We understand that brand changes can be difficult for people Before we changed the brand of lamotrigine from 1 May 2019, we got expert clinical advice from specialists and other healthcare professionals who currently help people manage living with epilepsy and mental health conditions Our expert clinical advisors have assured us that changing brands of lamotrigine is appropriate. We also checked with the New Zealand Transport Agency (NZTA) about changing brands of lamotrigine NZTA considered that a brand change is not a treatment change and that any risks would be extremely low

Most people shouldn't notice any difference when changing brands However, the chronic nature of epilepsy means people with the disease, even on treatment, can have recurrent and spontaneous seizures. A small number of people may not be able to change brands or may need to change back to their old brand, so may be eligible for our exceptional circumstances funding.

PHARMAC uses brand changes like this one to free up funding so that more medicines can be funded. This is how we meet our objective, set by legislation, of getting the best health outcomes from the funding that is available for pharmaceuticals.

I suggest your constituent be encouraged, if she hasn't already, to discuss her concerns with her healthcare professional. They will be aware of their patient's individual situation and medical history The health professional can apply for funding through our exceptional circumstances process if a brand change would not be suitable, or has not been tolerated. We have also agreed to fund a follow up appointment if this is required.

I appreciate you taking the time to write, please do not hesitate to contact me again if you require further information

Yours sincerely

Alison Hill
Director Engagement and Implementation

PHARMAC
TE PĀTAKA WHAIORANGA

Level 9, 40 Mercer Street, Wellington
PO Box 10254, Wellington 6143, New Zealand
P: +64 4 460 4990 | F: +64 4 460 4995
www.pharmac.govt.nz

29 August 2019

[redacted]

RE: Lamotrigine Brand Change

Thank you for your email dated 25 August

PHARMAC reads and considers all submissions received during the consultation process, as well as all Consumer Voice Feedback. All consultation responses were provided to the PHARMAC Board prior to making this decision We take steps to ensure that any potential issues arising from feedback are suitably addressed going forward.

For the proposal to move to one funded brand of lamotrigine, PHARMAC sought feedback from 29 August 2018 to 26 September 2018 After reviewing the feedback, we determined that more time was required to consider the issues raised before a decision could be made. The initial date put forward to implement the proposal was 1 December 2018 This date was delayed while we sought additional clinical advice from our expert clinical advisors (the Neurological and Mental Health Subcommittees) on the concerns that had been raised in feedback The Subcommittees considered the consultation feedback and updated evidence and concluded that there was no pharmacological reason to suggest there would be a clinical problem for patients with epilepsy or mental health conditions to change the brand of lamotrigine they use. The Subcommittees were supportive of the proposal to move to one funded brand of lamotrigine, and the implementation date was moved to 1 May 2019

Prescribers and pharmacists have been notified of the lamotrigine brand change through regular, well known channels. We have allowed five months between 1 May 2019 and 1 October 2019 for patients to have dialogue with their prescribers and pharmacists before changing to Logem We work hard to provide accurate and detailed information to prescribers and pharmacists, as well as to make the same information freely available on our website We are continuing to identify opportunities to work with health professionals and raise awareness of this brand change. The Best Practice Advocacy Centre have developed practical guidance for primary healthcare professionals who are supporting patients through this brand change, and we are highlighting this advice to the relevant health professionals Our enquiries team is also available to answer calls and emails from health professionals and consumers who have further questions. We can't estimate how many prescribers or pharmacists read our updates and notifications Similarly, with people who view information on our website, we can't estimate what proportion of those are primary healthcare professionals.

PHARMAC has created a specific process for considering funding for individual patients who, due to exceptional clinical difficulties, are unable to manage a change of brand Details on how to apply for Exceptional Circumstances funding are available on our website. Doctors can apply to PHARMAC before their patient has tried Logem (if they predict their patient would not be able to manage a change) or after their patient has tried Logem (if they consider their patient cannot manage the change) So far there have been three successful applications for ongoing funding of other brands of lamotrigine through this process.

PHARMAC cannot comment on an individual's clinical situation. PHARMAC makes decisions around which medicines are funded, but prescribers and pharmacists are best placed to use their clinical judgement in managing individual patients. While PHARMAC makes a range of funded options

available to New Zealanders, the final choice of medicine or brand is always at the discretion of the prescriber and the consumer

Yours sincerely,

Hannah Tibble-Gotz
Customer Support and Enquiries Management

Deirdre McCullough

From: Jane Wallace on behalf of Sarah Fitt
Sent: Monday, 26 August 2019 11:09 AM
To: [redacted]
Cc: 'David.Clark@parliament.govt.nz'
Subject: RE: Lamotrigine brand change casualties warning: graphic images

Dear [redacted]

Thank you for your email As you know, the sole supply period for the Logem brand of lamotrigine commences on 1 October 2019. People using other brands of lamotrigine have 5 months, starting from 1 May 2019, to change to the Logem brand

PHARMAC has created a specific process for considering funding for individual patients who, due to exceptional clinical difficulties, are unable to manage a change of brand. Details on how to apply for exceptional circumstances funding are available on our website Doctors can apply to PHARMAC before their patient has tried Logem (if they predict their patient would not be able to manage a change) or after their patient has tried Logem (if they consider their patient cannot manage the change) So far there have been three successful applications for ongoing funding of other brands of lamotrigine through this process.

We take reports of adverse events seriously. We strongly encourage anyone experiencing an adverse reaction to report this to CARM and talk to their health professional for advice Information on how to report a problem is on the Medsafe website. This can be completed by a patient, their family member or by a health professional.

As outlined in our letter to you on the 25th of July, if you would like to discuss your concerns with one of PHARMAC's medical directors please let us know and we will phone you at a time that suits you

Sarah Fitt | Chief Executive

PHARMAC | PO Box 10-254 | Level 9, 40 Mercer Street, Wellington

[redacted]

[redacted]

Exceptional Circumstances applications for Lamotrigine

An Exceptional Circumstances form and process has been set up to access applications for patients with exceptionally difficult to manage clinical circumstances which means they may not be able to transition to the funded lamotrigine (Logem).

This process was set up acknowledging that there will be some patients with Exceptional Circumstances who are unable to transition. Acknowledging that NPPA would not be the most appropriate pathway for these applications to be considered as it is unlikely applications would meet the principles of the NPPA policy.

Exceptional Circumstances fundi

Process

All Lamotrigine applications will require a clinical and a TGM view.

If the view of the Panel has been sought, then DMD is not required unless the FC or TGM considers it to be needed. If a DMD view is required all applications should go to DMD PM.

It is acknowledged that for some patients there may be funded treatments that they haven't tried, such as alternative AEDs. It is unlikely that we would push back on these treatments if the patient has history of stable and well controlled epilepsy. When assessing these applications, the main requirement to look at is whether the patient has exceptionally difficult to manage clinical circumstances which means they cannot transition to the Logem.

Applications that meet this threshold of "exceptionally difficult to manage" will be progressed for a decision using the EC framework. The NPPA decision paper template can be used for these decisions, however, will need adapting to remove the references to NPPA. Please see previous decision for an example.

For patients who do not meet the threshold of "exceptionally difficult to manage, a letter will be written to the applicant to communicate this outcome. A letter can be generated and completed using the general applicant letter in MAD.

Expert advice

A group of NPPA Advisory Panel members have been identified to provided clinical advice were needed on lamotrigine applications. This group is made up of [redacted]. Lamotrigine applications, which require Panel input, should go to all three of these advisors.

The record of the meeting to discuss the development of the EC lamotrigine process and form with these clinicians is here:

2019-04-04
conversation with P

Reporting

The Lamotrigine Project Team have requested a regular update regarding the applications at their fortnightly meeting. The update should include the number received, the number approved, the number that did not progress. A brief summary of what has been approved and what has been not progressed should be provided also.

This update should also be shared with the Panel members on a fortnightly basis.

PHARMAC MEDIA ENQUIRY

Date	28 September 2018
Subject	Lamotrigine
Media outlet & contact details	[redacted]
Deadline	COP 28 September 2018
Questions	Could Pharmac please advise us what it expects to be the percentage of patients taking lamotrigine who may experience problems with the proposed brand switch if it goes ahead?
Comms team lead	Matt W
Other staff input required (include names and contact details)	Bronwyn Locke Adrienne Martin
Spokesperson as required	Lisa Williams
Actions/response Other information (include key messages)	Consultation on the proposal to change to a single funded brand of lamotrigine closed on Wednesday this week, and PHARMAC is carefully considering all the feedback No decision has been made If the proposal is approved, up to 11,000 people would need to change their brand of lamotrigine to continue using a funded brand of this medicine. We are aware, from looking at 2017 dispensing data and a study published in 2014*, that many patients already switch between the three currently funded brands of lamotrogine. * https://www.ncbi.nlm.nih.gov/pubmed/25005492

Date complete	

[redacted]

Ref: C1802503

Dear [redacted]

Thank you for your emails of 19 and 26 September regarding funding of lamotrigine medications

PHARMAC is the Government agency that decides which pharmaceuticals will be publicly funded. PHARMAC operates independently of the Minister and Ministry of Health. This independence allows the public to have confidence in the impartiality of funding decisions. For this reason I am unable to intervene in PHARMAC's decision-making process

As you will be aware, PHARMAC sought feedback on 29 August 2018 for a proposed change to the funding of lamotrigine dispersible tablets used in the treatment of epilepsy and/or bipolar disorder.

Feedback on the proposal has now been closed and PHARAMC will be assessing all submissions before any decision is made. The information that GSK provided on the risks of stopping funding of lamotrigine medicines for epilepsy is important and will be used by PHARMAC's Board or delegate to determine the best health outcome for all New Zealanders.

Thank you for writing and sharing your concerns with me I wish GSK well in the work you are doing to improve health in New Zealand.

Yours sincerely

Hon Dr David Clark
Minister of Health

Deirdre McCullough

From: Lisa Williams
Sent: Thursday, 11 April 2019 3:59 PM
To: Lisa Williams
Subject: 2019-04-11 PHARMAC WEEKLY UPDATE part 2
Attachments: 2019 04 11 Decision to move to one funded brand of lamotrigine (Logem) pdf

Dear all, my apologies for a second email, there was a further item.

This decision about lamotrigine (see attached) will likely be of interest to DHB Chief Pharmacists.

For your additional interest and background, our dispensing data for 2018 shows that of all patients (12,500 patients in total) who collected a funded prescription for lamotrigine, around 50% (6,250) changed brands at least once during that year and around 4,000 patients changed brands two or more times We are not aware of, nor have we been informed of, any significant clinical impacts for these people when they changed brands.

Please forward this information to other individuals or groups who you think may be interested in this decision.

Warm regards

Lisa Williams | Director of Operations
[redacted]

Deirdre McCullough

From: Greg Williams
Sent: Thursday, 18 April 2019 10:40 AM
To: Adrienne Martin
Subject: FW: Lamotrigine
Attachments: Mylan Logem A4 Detail Aid APRIL 2019 pdf

FYI

Greg Williams | Manager, Procurement and Contracts

[redacted]
[redacted]

From: [redacted]
Sent: Wednesday, 17 April 2019 5:52 PM
To: Greg Williams [redacted]; Brian Roulston [redacted]
Cc: Felix Ram [redacted]
Subject: Lamotrigine

Dear Greg and Brian

Talking with my colleague [redacted] we thought you may find our GP detailer for Lamotrigine useful. Please find this attached showing biostudy data that we are 100% bioequivalent to GSK's Lamictal (Key clinical parameters: AUC = 101% and Cmax = 100%). Please feel free to use this information however you may wish to support messages around bioequivalence etc

If you need any further information on Mylan's product please don't hesitate to reach out to either of us.

Kind regards

[redacted]

[redacted]

Deirdre McCullough

From: Donna Jennings on behalf of Web Enquiry
Sent: Tuesday, 30 April 2019 4:44 PM
To: [redacted]
Subject: RE: Query Lamotrigine brand change over

Hi [redacted]
Sorry about the delay in getting back to you on this one.

People who make submissions about brand changes are not routinely notified of the final decision – however, the decision will always be published on our website.
You can ask to be added to the notification list – for a particular interest area – although you will end up with a whole lot of emails.

When we publish the decision notification online we include a summary of the submission feedback at the end. This is usually grouped in themes as many responses will have the some comments – if your comment/question hasn't been included in there, or you would like more information or clarification, get in touch with us.

Re news article. Yes, we have made it easier for doctors to apply to us in exceptional circumstances. There is now more info about this, including the form, on the lamotrigine my medicine has changed webpage

Kind regards
Donna

F[redacted]

[redacted]

The Sole Supply period doesn't start until 1 October 2019, this means there will be another five months for people to change to the Logem brand.

The decision has been sent out to a lot of interested parties. And we update pharmacists every month about upcoming changes – the update for 1 May changes will go out on Thursday

As you will be aware we don't have direct access to consumers however, the five month transition will ensure there is time to support people changing brands.

We have been working with consumer advocacy groups and primary care organisations.

We already have info up on our website My Medicine Has Changed page. More info is expected to go up on here in the coming weeks

Let us know if you have further concerns or questions about this change

Kind regards

Donna Jennings

PHARMAC

[redacted]

Deirdre McCullough

From: Karen Jacobs-Grant
Sent: Tuesday, 23 April 2019 12:43 PM
To: [redacted]
Cc:
Subject: Lamotrigine brand to change information attached

Tēnā koutou katoa,

Brand change for Lamotrigine

Lamotrigine is a medicine used to help manage epilepsy and some mental health conditions such as bipolar disorder.

A decision made by PHARMAC to the change supplier of lamotrigine tablets means that whānau who are currently taking the Lamictal brand of lamotrigine, will need to change brands to Logem, from 1 May 2019. They will have five months to do this to ensure a continued supply of their medicine.

This decision means that:

- from 1 October there will be only one funded brand of lamotrigine 25 mg, 50 mg and 100 mg dispersible tablets (Logem), rather than three different brands (Lamictal, Arrow-Lamotrigine and Logem)
- whānau will be able to collect a three-month supply of Logem from their community pharmacy.
- whānau who are not already using the Logem brand, will have five months to change to it.

There are no changes to the funding of lamotrigine 2 mg (Lamictal) and 5 mg (Lamictal and Arrow Lamotrigine) dispersible tablets, except that people will be now be able to collect a three-month supply of these from their community pharmacy.

In summary

- The funded brand of lamotrigine is changing from Lamictal, Arrow-Lamotrigine and Logem to Logem only.
- From **1 May 2019 to 30 September 2019,** whānau will have five months to change to the Logem brand of lamotrigine
- From **1 October 2019** PHARMAC will only fund the Logem brand of lamotrigine
- There is no change to the funding of the 2 mg and 5 mg presentations of lamotrigine used for young children. They would not need to change their brand of lamotrigine.

We know that changing brands of medicines can be difficult for some whānau It's understandable that they might have questions about changing their medicines.

Resources to help changing brands

There is a number of resources and information available for health professionals, consumer organisations and patients to support the lamotrigine medicine brand change Further details will be made available from PHARMAC's website

In addition,

- There will be a mechanism under the PHARMAC exceptional circumstances framework for prescribers to apply for their patient to remain on their current brand of lamotrigine. This is for those patient's with exceptionally difficult circumstances who prescribers think would not manage this brand change or have not tolerated the change.

- If whānau require extra visits to their GP over and above their usual visits to manage the change in brand, GP clinics can apply to PHARMAC to cover patients' out of pocket costs.

PHARMAC's job is to make sure that New Zealanders have access to the medicines they need. Making brand changes to medicines helps us achieve that by freeing up money to fund other medicines

Reducing the number of brands of lamotrigine we fund will **free up more than $30 million** over the next five years; money that PHARMAC will use to fund other medicines for all New Zealanders.

For more information-https://www pharmac govt nz/news/notification 2019-04 11 lamotrigine/

To contact PHARMAC, either phone **Enquiries on 0800 660 050** or email us at enquiry@PHARMAC.govt.nz

Ngā mihi nui

Karen

Karen Jacobs Grant | Senior Advisor Māori Responsiveness
Ngāti Whātua, Ngāpuhi, Ngāti Torehina

Te Pātaka Whaioranga - PHARMAC | PO Box 10-254 | The Terrace, Wellington 6143
Level 9, 40 Mercer Street, Wellington 6011
[redacted]
www pharmac health nz

Deirdre McCullough

From: Web Enquiry
Sent: Wednesday, 1 May 2019 3:44 PM
To: [redacted]
Subject: Lamotrigine brand change

Kia ora [redacted]

Thank you for getting in touch with us about the lamotrigine brand change

Firstly, we're sorry to hear about your daughter's situation. This must be a distressing time for you and your family.

I'd like to assure you that before we changed brands, we got expert clinical advice from healthcare professionals who manage people living with epilepsy and mental health conditions to make sure it's appropriate for people to change brands of lamotrigine. Our expert clinical advisors have assured us that changing brands of lamotrigine is appropriate

We're also working with doctors, pharmacists and patients to make sure everyone is supported through this change However, I understand that this has not been the case for you and am sorry to hear that your daughter's neurologist was unaware of the brand change.

Before we made a decision to change brands, we ran a thorough consultation process asking for feedback from healthcare professionals, patient advocacy groups and patients A summary of the feedback we received and our response to this is available on our website: https://www.pharmac.govt.nz/news/notification 2019-04 11 lamotrigine/

I understand that the consultation document has caused some confusion. The intent of our consultation was not to suggest that children only take 2 mg and 5 mg lamotrigine It was to highlight that these strengths are mainly used by children.

You may be interested to know that we did receive feedback from carers of children and adolescents with epilepsy, which was considered by our clinical advisors. Our clinical advisors were also aware that children may have to change brands. They considered that some children with epilepsy may have trouble with a brand change, depending on their individual circumstances, but that these patients should already be under the care of a specialist who could help them through the change

You can read a summary of their advice on our website: https://www pharmac govt nz/assets/ptac-neurological and-mental health-subcommittee-lamotrigine-minute 2019-02 .pdf

We do have a process to consider funding for individuals in exceptional circumstances. If you would like, we would be more than happy to share this information with your daughter's neurologist.

We also have more information available on our website, which explains what this brand change means, as well as information about the exceptional circumstances process: https://www pharmac govt nz/medicines/my-medicine-has-changed/lamotrigine/

Once again, thank you for taking the time to share your concerns with us. If you would like more information, please don't hesitate to ask.

Ngā mihi nui
Katie

Deirdre McCullough

From: Web Enquiry
Sent: Tuesday, 7 May 2019 10:30 AM
To: [redacted]
Subject: Lamotrigine brand change - response to Facebook messenger

Kia ora [redacted]

Thanks for following up with us about the lamotrigine brand change

Before deciding to change brands of lamotrigine, we sought extensive clinical advice from two Subcommittees, both the Mental Health Subcommittee and Neurological Subcommittee. Both Subcommittees have practicing expert healthcare professionals who manage people, including children, living with epilepsy and mental health conditions. We also encouraged members of our Subcommittees to discuss items with their colleagues, as we're aware that Subcommittees can't meet all subspecialties. Our experts were aware that this brand change may impact children and have assured us that changing brands of lamotrigine is appropriate

Children are involved in most decisions we make, so I can assure you that our clinical advisors take this very seriously We have every confidence that if our advisors had any concerns for children or other groups of people, these concerns would have been raised and recorded in their meeting minutes. If this change wasn't appropriate for children, we would not have made this decision

You can read the full minutes on our website: https://www pharmac govt nz/assets/ptac neurological and mental health-subcommittee-lamotrigine minute 2019-02 .pdf

I appreciate your concern about changing brands. I do encourage you to talk to your daughter's neurologist as they're the best person to talk to about this change. As I've offered before, we are also more than happy to call both you and your daughter's neurologist to talk about this brand change and how we can help

Ngā mihi nui
Katie

PHARMAC
TE PĀTAKA WHAIORANGA

Level 9, 40 Mercer Street, Wellington
PO Box 10254, Wellington 6143, New Zealand
P: +64 4 460 4990 | F: +64 4 460 4995
www.pharmac.govt.nz

Kia ora[redacted]

Thanks for getting in touch with us.

The advice we got from our expert clinical advisors is that you shouldn't notice any difference when using different, and switching between, brands of lamotrigine.

If you have any concerns, we do recommend that you speak to your doctor or pharmacist. We'd also be more than happy to speak with you about this over the phone we have trained pharmacists on the line who can help explain what this brand change means

Ngā mihi nui
Katie

Deirdre McCullough

From: Adam McRae
Sent: Thursday, 30 May 2019 11:29 AM
To: Adrienne Martin; Web Enquiry
Cc: Peter Murray
Subject: RE: lamotrigine

I am in two minds about promoting the co-payment fee reimbursement here as the GP may not agree to it or she maybe under the care of her Neuro and this isn't her chief concern. I think maybe saying inserting this to close out the email:
*"Given your specific circumstances, including medication hypersensitivities and the requirement for periodic dose changes, we would also encourage you to have a discussion with your prescriber "
Cheers
A

From: Adrienne Martin
Sent: Thursday, 30 May 2019 11:12 AM
To: Web Enquiry <enquiry@Pharmac.govt.nz>
Cc: Adam McRae [redacted] Peter Murray [redacted]
Subject: FW: lamotrigine

Suggested response below.
You might also like to run this via an MD before we sent it out. Pete have copied you in see what you think.

Thanks
A

Dear [redacted]

Thanks for your follow up email. Hopefully the below information helps to answers your questions.

I'm sorry I cannot confirm for you specific details of the clinical trials What I can confirm for you is that our clinical experts have thoroughly reviewed all of the clinical trials identified and based on the available evidence, they concluded that there was no pharmacological reasons to suggest there would be a clinical problem with changing brands of lamotrigine for patients with epilepsy or mental health. The Subcommittee were aware that there would be could be two brands of lamotrigine 5 mg tablets (Lamictal and Arrow-Lamotrigine) and one brand of 25 mg, 50 mg and 100 mg tablets (Logem) at the end of the brand change transition period (ie people taking mixed brands could be a possibility) when they considered the evidence. A list of the clinical trials that were considered is provided in the minutes from the link below I have not detailed them to you in this email, as I am sure you can appreciate it is a long list, but you (or your healthcare professional) can access them yourself should you choose to.

https://www.pharmac.govt.nz/assets/ptac neurological and-mental-health subcommittee-lamotrigine minute-2019-02-.pdf

We rely on the clinical advice provided by our expert Committees to help us ensure that we are making the right decisions when it comes to brand changes For your information the clinical experts that advised us on this brand change were from the Neurological Subcommittee and Mental Health Subcommittee which is made up of Neurologists, Psychiatrists and General Physicians from around the country Details about who is on each Subcommittee is available on our website.

As you highlight in your email Logem is bioequivalent to Lamictal. This has been assessed by Medsafe. Medsafe is the New Zealand Medicines and Medical Devices Safety Authority. It is responsible for the regulation of medicines,

ensuring they are acceptably safe. You can read more about Medafe from its website. However, even though Medsafe have assessed Logem as being bioequivalent to Lamictal, we are aware from the clinical advice that our experts provided us that people with epilepsy need support through any brand change. [redacted]

[redacted]

Thanks
Adrienne

Adrienne Martin | Senior Therapeutic Group Manager/ Team Leader

PHARMAC, PO B... 10254, L... 18 40 M... St... L W ... N...
[redacted]
[SEEMail]

From: Web Enquiry <enquiry@Pharmac.govt.nz>
Sent: Tuesday, May 28, 2019 2:01 PM
To: Adrienne Martin <[redacted] Adam McRae <[redacted]
Subject: FW: lamotrigine

Hey Adrienne

Could you please help us develop a response? See the chain below.

Cheers
Katie

[redacted]

On Tue, 28 May 2019 at 13:22, Web Enquiry <enquiry@pharmac.govt.nz> wrote:

> Kia ora [redacted]

Thanks for getting in touch with us.

The advice we got from our expert clinical advisors is that you shouldn't notice any difference when using different, and switching between, brands of lamotrigine

If you have any concerns, we do recommend that you speak to your doctor or pharmacist. We'd also be more than happy to speak with you about this over the phone – we have trained pharmacists on the line who can help explain what this brand change means.

Ngā mihi nui

Katie

[redacted]

Deirdre McCullough

From: Jan Carey
Sent: Thursday, 13 June 2019 3:59 PM
To: [redacted]
Subject: RE: Medicine funding - why am I unable to contact any of your phone lines at 220pm on Wed

Hello [redacted]

Thank you for your email I am sorry I was not able to answer your call, or contact you by phone

As you are aware, the funded brand of lamotrigine is changing from Lamictal, Arrow-Lamotrigine, and Logem to Logem only. From 1 May 2019 to 1 October 2019 people will have five months to change to the Logem brand of lamotrigine. Medsafe have confirmed that Logem works in the same way as the previously funded brand, Lamictal (is bioequivalent).

PHARMAC sought extensive advice from healthcare professionals who manage people living with epilepsy and mental health conditions, such as Neurologists, Psychiatrists and GPs. Our clinical experts carefully considered all feedback from everyone who responded to the consultation – along with all the published clinical studies and other available evidence about brand changes for lamotrigine before confirming it would be appropriate for people to change brands. Our expert clinical advisors have assured us that changing brands of lamotrigine is appropriate. We have taken all feedback into account and have developed a comprehensive implementation plan to support everyone through this change. This decision would not have been made if our expert clinical advisors were not supportive of this change, regardless of the money it could free up

For more information about the evidence and research our experts assessed and what they discussed, here is the link to the information on our website: https://www.pharmac.govt.nz/assets/ptac-neurological-and-mental-health-subcommittee-lamotrigine-minute 2019-02 pdf

For more information about our expert clinical advisors on the Neurological Subcommittee and Mental Health Subcommittee, visit our website: https://www pharmac govt nz/about/advice/ptac-subcommittees/

PHARMAC understands that change can be difficult for some people. It's understandable that people might have questions about changing brands, but they shouldn't notice any difference when changing to Logem If people have any questions or concerns about changing their brand of lamotrigine, we are encouraging them to talk with their healthcare professionals .Some people may return to their GP with concerns following the change to the Logem brand and need additional support to make a successful change. In these cases, the GP visit co payment may be waived and PHARMAC will reimburse the GP clinic.

In addition, there is a mechanism for prescribers to apply for their patient to remain on their current brand of lamotrigine. This would be for those patients who, due to exceptional clinical difficulties, are unable to manage a change to the Logem brand, or who have not tolerated the change A copy of the application form is available here https://www.pharmac.govt.nz/assets/lamotrigine exceptional-circumstances-form.doc.

I hope this information is helpful.

Best wishes

Jan Carey
PHARMAC

From: [redacted]
Sent: Wednesday, 5 June 2019 2:28 PM

Deirdre McCullough

From: Jan Carey
Sent: Friday, 7 June 2019 1:49 PM
To: [redacted]
Subject: RE: Change from Brand Lamictal R to generic Lamotrigine

Hello [redacted]

Thank you for taking the time to contact us and share your story

PHARMAC's role within the New Zealand health system is to make decisions on which medicines and medical devices are funded in order to get the best health outcomes from within the available funding.
This applies to *all* New Zealanders.

Medsafe, part of the Ministry of Health, decides which pharmaceuticals are safe and effective for New Zealanders to use They have confirmed that Logem works in the same way as the previously funded brands, Lamictal and Arrow Lamotrigone. (is bioequivalent).

PHARMAC sought extensive advice from healthcare professionals who manage people living with epilepsy and mental health conditions, such as Neurologists, Psychiatrists and GPs
Our clinical experts carefully considered all of the feedback from everyone who responded to the consultation – along with all the published clinical studies and other available evidence about brand changes for lamotrigine - before confirming it would be appropriate for people to change brands. Our expert clinical advisors have assured us that changing brands of lamotrigine is appropriate.
We've taken all feedback on board and have developed a comprehensive implementation plan to support everyone through this change.

We wouldn't have made this decision if our expert clinical advisors were not supportive of this change, regardless of the money it could free up

For more information about the evidence and research our advisors assessed and what they discussed, please visit our website:
https://www.pharmac.govt.nz/assets/ptac-neurological-and-mental-health-subcommittee-lamotrigine-minute-2019-02 .pdf

For more information about our expert clinical advisors on the Neurological Subcommittee and Mental Health Subcommittee, visit our website: https://www.pharmac.govt.nz/about/advice/ptac-subcommittees/

There is a mechanism for prescribers to apply for their patient to remain on their current brand of lamotrigine. This would be for those patients who, due to exceptional clinical difficulties, are unable to manage a change to the Logem brand, or who have not tolerated the change. A copy of the application form is available here https://www pharmac govt nz/assets/lamotrigine exceptional-circumstances-form doc

If this is not successful, it may be possible for you to still obtain Lamictal unfunded. I have had anecdotal information that GSK are intending to continue to bring Lamictal into New Zealand after 1 October You may wish to contact them on 09 3672900.

I am very concerned with your comment about suicide I know change can be difficult I understand that you will have questions about changing brands, but you shouldn't notice any difference when changing to Logem. Please

do talk to your doctor about the change and any associated feelings. If you return to their GP with concerns following the change to the Logem brand and need additional support to make a successful change, the GP visit co-payment may be waived.

I hope this information is helpful and goes some way to providing reassurance to you

Take care.

Kind regards

Jan Carey
PHARMAC

[redacted]

Deirdre McCullough

From: Jan Carey
Sent: Wednesday, 3 July 2019 4:30 PM
To: [redacted]
Subject: RE: lamotrigine

Hello [redacted]

Thank you for your follow up email I acknowledge your main concern, that, as Logem doesn't come in all strengths that may be required to get the correct dose, the two brands may need to be to be taken together.

Medsafe have confirmed that Logem and Lamictal both contain the same active ingredients.

When we considered this brand change, we realised some people would need to use two brands at the same time to get the required dose Because of this, we sought advice from our Neurological subcommittee The subcommittee is made up of specialists including neurologists who work with New Zealand patients every day. The subcommittee discussed the issue of brand mixing and advised us that they had no concerns

Please continue to discuss the concerns you have with your doctor.. They know your clinical situation best. As you are aware, we have created a specific Named Patient Pharmaceutical Assessment process for this change This gives prescribers a way to apply for funding of an alternative brand, should their patient have clinical circumstances that we haven't considered We have told prescribers and pharmacists about this process A copy of the application form they can use for this is available here https://www.pharmac.govt.nz/assets/lamotrigine-exceptional-circumstances-form.doc. Your doctor will be able to assess whether it would be appropriate to use this process

We are continuing to work with health professionals and organisations, including Epilepsy New Zealand, about this change We are keeping health professionals fully informed about it and they will, in turn, talk to their patients about the change and what it means for them. We have allowed five months for this change to ensure people have plenty of time to discuss any issues with their doctor or pharmacist before they need to change

We take brand changes very seriously, and expert clinical advice is key to our decision making I hope this information goes some way to addressing your concerns.

I wish you all the best.

Kind regards

Jan

[redacted]

[redacted]

Dear [redacted]

Thanks for your follow up email I am replying on behalf of Katie I hope the information below helps to answers your questions.

I'm sorry I cannot confirm for you specific details of the clinical trials. What I can confirm for you is that our clinical experts have thoroughly reviewed all of the clinical trials identified and based on the available evidence, they concluded that there were no pharmacological reasons to suggest there would be a clinical problem with changing brands of lamotrigine for patients with epilepsy or mental health. The Subcommittee were aware that there could be two brands of lamotrigine 5 mg tablets (Lamictal and Arrow-Lamotrigine) and one brand of 25 mg, 50 mg and 100 mg tablets (Logem) at the end of the brand change transition period (ie people taking mixed brands could be a possibility) when they considered the evidence. A list of the clinical trials that were considered is provided in the minutes from the link below I have not detailed them to you in this email, as I am sure you can appreciate it is a long list, but you (or your healthcare professional) can access them yourself should you choose to.

https://www.pharmac.govt.nz/assets/ptac neurological and mental health subcommittee-lamotrigine minute-2019-02 pdf

We rely on the clinical advice provided by our expert Committees to help us ensure that we are making the right decisions when it comes to brand changes The clinical experts that advised us on this brand change were from the Neurological Subcommittee and Mental Health Subcommittee which is made up of Neurologists, Psychiatrists and General Physicians from around the country Details about who is on each Subcommittee is available on our website.

As you highlight in your email Logem is bioequivalent to Lamictal This has been assessed by Medsafe Medsafe is the New Zealand Medicines and Medical Devices Safety Authority. It is responsible for the regulation of medicines, ensuring they are acceptably safe You can read more about Medafe from its website However, even though Medsafe have assessed Logem as being bioequivalent to Lamictal, we are aware from the clinical advice that our experts provided us that people with epilepsy need support through any brand change. Given your specific circumstances, including medication hypersensitivities and the requirement for periodic dose changes, we would also encourage you to have a discussion with your prescriber.

Best wishes

Jan Carey

PHARMAC

[redacted]

On Tue, 28 May 2019 at 13:22, Web Enquiry <enquiry@pharmac.govt.nz> wrote:

Kia ora [redacted]

Thanks for getting in touch with us

The advice we got from our expert clinical advisors is that you shouldn't notice any difference when using different, and switching between, brands of lamotrigine.

If you have any concerns, we do recommend that you speak to your doctor or pharmacist. We'd also be more than happy to speak with you about this over the phone – we have trained pharmacists on the line who can help explain what this brand change means

Ngā mihi nui

Katie

[redacted]

PHARMAC
TE PĀTAKA WHAIORANGA

Level 9, 40 Mercer Street, Wellington
PO Box 10254, Wellington 6143, New Zealand
P: +64 4 460 4990 | F: +64 4 460 4995
www.pharmac.govt.nz

25 July 2019

[redacted]

Cc: Hon. David.Clark@parliament.govt.nz; askmedsafe@health.govt.nz

Dear [redacted]

Lamotrigine brand change

Thank you for your latest email of 9 July, about the lamotrigine brand change. I am sorry that you are not satisfied with my response to your earlier letter on the lamotrigine brand change

The Neurological Subcommittee specifically considered the issue of brand and dosage mixing that you are concerned about. The Subcommittee could see no problem with having different suppliers for the adult strength and the paediatric strength preparations of lamotrigine tablets.

While I am happy to continue to answer your questions by writing, would you like to talk through your concerns with one of our medical directors? If you would, please let me know a few dates that would suit you, and whether you would like to do this in person in Wellington, or as a phone call

Yours sincerely

Sarah Fitt

Sarah Fitt
Chief Executive

PHARMAC
TE PĀTAKA WHAIORANGA

Level 9, 40 Mercer Street, Wellington
PO Box 10254, Wellington 6143, New Zealand
P: +64 4 460 4990 | F: +64 4 460 4995
www.pharmac.govt.nz

9 July 2019

[redacted]

Dear [redacted]

Re: Lamotrigine brand switch

Thank you for your letter of 21 June expressing your concerns about the change in your daughter's medication and in particular concerns around mixing two brands of lamotrigine, Logem and Lamictal.

When we considered this brand change, we realised some patients may need to use two brands at the same time to get the required dose. Because of this, we sought clinical advice from our Neurology Subcommittee. The Neurological Subcommittee is made up of specialists including Neurologists and General Practitioners, who work with New Zealand adult and paediatric patients every day.

The Subcommittee discussed the issue of brand mixing and advised us they had no concerns. I'm sorry that the minutes from the Neurological Subcommittee meetings do not cite any particular published evidence to address your concerns, but I can assure you that mixing two brands was considered.

We would be happy to speak with your pharmacist and/or your daughter's neurologist about the issue and any concerns they may have about mixing brands.

As you are aware, we have created a specific Named Patient Pharmaceutical Assessment process for this change. This gives prescribers a way to apply for funding of an alternative brand, should their patient have clinical circumstances that we haven't considered. We have told prescribers and pharmacists about this process.

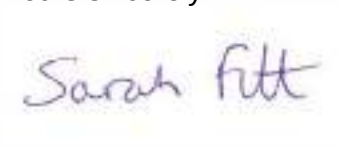
A copy of the application form they can use for this is available here https://www.pharmac.govt.nz/assets/lamotrigine-exceptional-circumstances-form.doc.

Your daughter's doctors will be able to assess whether it would be appropriate in her case to use this process. Given the concerns you have raised we would encourage you to discuss this with your daughter's doctor.

We are continuing to work with health professionals and organisations, including Epilepsy New Zealand, about this change. We are keeping health professionals fully informed about it and they will, in turn, talk to their patients about the change and what it means for them. We have allowed five months for this change to ensure people have plenty of time to discuss any issues with their doctor or pharmacist.

We take brand changes very seriously, and expert clinical advice is key to our decision making. I hope this information goes some way to addressing your concerns.

Yours sincerely



Sarah Fitt
Chief Executive

Deirdre McCullough

From: Web Enquiry
Sent: Thursday, 11 July 2019 2:54 PM
To: [redacted]
Subject: RE: Lamotrigine brand change question

Hello [redacted]

Thank you for your email

You can apply to PHARMAC under the exceptional circumstances framework for continued funded access to Lamictal for your patient.

This is for people who, due to exceptional clinical difficulties, are unable to manage a change to the Logem brand, or who have not tolerated the change during the transition period. There is a specific form for clinicians to complete. The link is here:

https://www pharmac govt nz/tools resources/forms/

I hope this information is helpful.

Kind regards

Jan Carey
PHARMAC

From: [redacted] (ADHB) [redacted]
Sent: Thursday, 11 July 2019 11:59 AM
To: Web Enquiry <enquiry@Pharmac.govt.nz>
Subject: Lamotrigine brand change question

Dear Pharmac

A patient of mine has experienced loss of seizure control resulting in brief daily seizures on transitioning to the new brand
She is on a maximal dose already of lamotrigine

How do we obtain funding for her to go back on to her previous brand Lamictal

Thank you
[redacted]

PHARMAC
TE PĀTAKA WHAIORANGA

MEMORANDUM FOR BOARD MEETING 29 MARCH 2019

To: PHARMAC Directors

From: Chief Executive

Date: March 2019

Proposal to move to one funded brand of lamotrigine (Logem)

Recommendations

It is recommended that having regard to the decision-making framework set out in PHARMAC's Operating Policies and Procedures you:

resolve to approve the changes to the Pharmaceutical Schedule outlined in Appendix One;

resolve to approve the 29 August 2018 provisional agreement with Mylan New Zealand Limited, as subsequently amended on 7 March 2019;

note the summary of consultation feedback and full copies of consultation responses (Appendix Four);

resolve that the consultation on this proposal was appropriate, and no further consultation is required; and

note the proposed implementation activities should the proposal be approved (Appendix Two)

SUMMARY OF PHARMACEUTICAL			
Brand name	Logem	**Chemical name**	Lamotrigine
Therapeutic Group	Nervous System – Antiepilepsy Drugs Control of Epilepsy	**Presentation**	Tab 25 mg, 50 mg and 100 mg
Supplier	Mylan	**Pharmaceutical type**	Generic
MoH Restriction	Prescription medicine	**Application date**	N/A
Section F	No	**Original pack**	No
Proposed restriction	N/A		

Brand - Formulation - Packsize	**Current subsidy**	**Proposed subsidy**	**Proposed Price**
Logem – Tab 25 mg – 56 tablets	$19.38	$2.76	$2.76
Logem – Tab 50 mg – 56 tablets	$32.97	$3.31	$3.31
Logem – Tab 100 mg – 56 tablets	$56.91	$4.40	$4.40

Market data **Year ending**	**30 Jun 2019**	**30 Jun 2020**	**30 Jun 2021**
Community Subsidy (gross)	$9,430,000	$2,910,000	$910,000

[redacted]

Notes:
1. Subsidy (gross) = forecast of spending on lamotrigine at the proposed subsidy
2. Net community pharmaceutical cost = forecast of change in total spending on funded pharmaceuticals claimed via CPB compared with status quo.
3. Net hospital pharmaceutical cost = forecast of change in hospital expenditure on funded pharmaceuticals.
4. Net distribution costs = forecast costs related to markup and distribution and other non-pharmaceutical costs (community and hospital).
5. Other DHB costs = forecast costs related to the change to stat dispensing
6. Total net cost to DHBs = forecast of change in spending for community and hospital pharmaceuticals compared with status quo, including distributions costs.
7. All pharmaceutical costs are ex-manufacturer
8. All costs are net and ex-GST.
9. NPV = net present value and is calculated over 5 years using an annual discount rate of 8%.
10. Calculations are in A1246104

Executive Summary

- Lamotrigine is an anticonvulsant and is predominantly used for the treatment of epilepsy and some mental health conditions, e.g. bipolar disorder, behavioural disorders and schizoaffective disorder

- PHARMAC currently funds three brands of lamotrigine: Lamictal (supplied by GSK), Logem (supplied by Mylan) and Arrow-Lamotrigine (supplied by Teva), at a total annual net cost of [redacted]

- There are approximately 12,500 people taking lamotrigine and around 42% of patients are taking it for epilepsy with the other 58% taking it for a mental health condition or other indication.

- The proposal is to award sole supply in the community and DHB hospitals to Mylan's brand of lamotrigine 25 mg, 50 mg and 100 mg dispersible tablets (Logem). This is a result of a 2018 Request for Proposals (RFP) process. Implementation would be over a 5-month period beginning 1 May 2019

- The effect of the proposal would mean that all people taking any other funded brand of lamotrigine 25 mg, 50 mg and 100 mg dispersible tablets (Lamictal and Arrow-Lamotrigine) would have 5 months to transition to the Logem brand. This would result in approximately 11,000 people (89% of all lamotrigine patients) changing brands.

- Consultation responses from healthcare professionals were generally supportive of the proposal. However, concerns regarding the potential for loss of seizure control or mood destabilisation were raised by consumers, consumer groups, pharmaceutical suppliers and Medsafe.

- Due to these concerns we sought further advice from both the Neurological Subcommittee and Mental Health Subcommittee, in particular around the feedback from Medsafe. Both Subcommittees, having considered the consultation feedback and other material presented to them, remained supportive of the proposal to move to one funded brand of lamotrigine (Logem), with appropriate implementation support.

- We note that we would be implementing a brand change without Medsafe's support Through meeting with Medsafe and exchanges of information, Medsafe's position has somewhat evolved; however, some of their concerns remain. PHARMAC staff note the differing views of Medsafe and our specialist Subcommittees We consider that we have taken sufficient clinical advice from our Subcommittees (which comprehensively reviewed the information provided by Medsafe) on the clinical risks associated with a brand change of lamotrigine and, based on the Subcommittees' advice, we are supportive of the proposal to change to one funded brand of lamotrigine (Logem), and have developed a comprehensive implementation plan to support the brand change and manage potential and perceived clinical risks (refer to Appendix Two)

- Should the proposal be approved it would mean significant savings, of approximately [redacted] over 5 years to DHBs

Why Proposal Not Decided Under Delegated Authority

The proposal outlined in this Board paper has not been dealt with by the Chief Executive under delegated authority because:

- the estimated Financial Impact (NPV) of this proposal is more than $10,000,000 of the Pharmaceutical Budget, and
- the proposal is considered contentious due to perceived and potential clinical risks of a brand change in this population

The Financial Impact is calculated on the basis of the net present value (NPV) of the proposed subsidy (ex manufacturer exclusive of GST) over 5 years at a discount rate of 8% to be paid by the funder for the product(s) and the forecast demand, taking into account any effect of the change/decision on that demand, versus the status quo.

The Proposal

This proposal is to award sole supply of lamotrigine 25 mg, 50 mg and 100 mg dispersible tablets to Mylan for its brand of lamotrigine tablets (Logem) This proposal arose from a RFP dated 14 June 2018. If approved, this proposal would mean that ~11,000 people with epilepsy and mental health conditions would need to change brands of lamotrigine.

Key details of the proposed changes are as follows:

- The price and subsidy of Mylan's brand of lamotrigine (Logem) would be reduced on 1 May 2019
- All other currently funded brands (Lamictal and Arrow) would remain listed and fully funded for a 5-month transition period beginning on 1 May 2019 and would be delisted on 1 October 2019 This transition period differs from the one set out in the original provisional agreement with Mylan and in the consultation letter, which included a period of reference pricing We have made these changes, with support of the supplier, as a result of consultation feedback to support patients through the transition
- Following the transition period Logem would have sole subsidised supply until 20 June 2022
- [redacted] PHARMAC would consider applications for those patients who are not able to change brands through our exceptional circumstances framework, via a specially designed application form for lamotrigine.
- No changes are proposed for the paediatric presentations (2 mg and 5 mg dispersible tablets). These would remain listed and fully funded.
- The dispensing frequency of all presentations of lamotrigine would be changed from 'may be dispensed three monthly if endorsed accordingly' to three-monthly dispensing (stat) from 1 October 2019. This is in response to consultation feedback we have received that this may help with adherence for people with epilepsy

A copy of the provisional agreement with Mylan subsequentially amended on 7 March 2019 can be provided to any Board member on request

Background to Proposal

Lamotrigine is indicated for the treatment of epilepsy and for the prevention of mood episodes in patients with bipolar disorder, predominantly by preventing depressive episodes In addition, the clinical advice we have received indicates that patients are likely to also be prescribed lamotrigine for behavioural disorders, schizoaffective disorder and a small number of patients could also be taking it for trigeminal neuralgia

PHARMAC currently funds three brands of lamotrigine: Lamictal (GSK), Logem (Mylan) and Arrow-Lamotrigine (Teva) at a total annual net cost of [redacted]

There are approximately 12,500 patients taking lamotrigine, 62% of whom are on Lamictal brand, 26% on the Arrow-Lamotrigine brand and 12% on the Logem brand. Based on our analysis approximately 42% of patients are taking lamotrigine for epilepsy and approximately 58% are taking lamotrigine for a mental health or other indications such as trigeminal neuralgia. Because there are multiple brands currently listed, changing brands can and does currently occur at a pharmacy level

We acknowledge that epilepsy has a significant impact on patients' quality of life, in that activities such as employment, driving and social interaction are dependent on control of the condition Consequences of uncontrolled seizures can be severe (death, severe injury, drowning, loss of driver's licence for up to 12 months). In addition, a patient having a seizure while driving could cause harm to themselves or other people. We have engaged and consulted with the New Zealand Transport Agency (NZTA) on this particular aspect, in the context of a person's fitness to drive, and in summary they were not concerned as they consider the proposal would result in a change of brand, as opposed to a change in treatment

The chronic nature of the disease means that people with epilepsy, even on treatment, can have recurrent and spontaneous seizures. We are aware that a brand change that coincides with a patient being destabilised or having a spontaneous seizure could be perceived to be due to the change in brand. Due to this, historically, there has been considerable resistance expressed by clinicians to changes in this market. In response PHARMAC has, up to this point, taken a more conservative approach to manage expenditure for the majority of antiepileptic medicines. However, more recent clinical studies and international recommendations for brand changes in this market have provided further evidence to support these commercial activities.

PTAC and relevant Subcommittees have provided clinical advice multiple times around brand changes for anti-epileptic drugs (AEDs). Both the Neurological Subcommittee and the Mental Health Subcommittee advised us that it would be clinically acceptable to progress with a competitive process for lamotrigine that could involve a brand change for some or all patients

The opportunity for significant savings led us to run a RFP for sole supply of lamotrigine. This was informed by advice/support from both Neurological and Mental Health Subcommittees. The RFP was run in June 2018 and a preferred proposal, estimated to provide savings of [redacted] (NPV) over 5 years to DHBs, was selected for sole supply of Logem.

In August 2018, PHARMAC issued a consultation on a proposal to move to one funded brand of lamotrigine (Logem) following a transition starting on 1 December 2018 Healthcare professionals were generally supportive of the proposal. However, concerns regarding the potential for loss of seizure control or mood destabilisation were raised by consumers, consumer groups, pharmaceutical suppliers and Medsafe

Funding history and current funding arrangements

[redacted] there are currently multiple funded brands of lamotrigine listed without restrictions. The currently funded brands and strengths of lamotrigine are shown in the table below

LAMOTRIGINE	Brand
Tab dispersible 2 mg	**Lamictal**
Tab dispersible 5 mg	**Arrow-Lamotrigine** **Lamictal**
Tab dispersible 25 mg	**Arrow-Lamotrigine** **Lamictal** **Logem**
Tab dispersible 50 mg	**Arrow Lamotrigine** **Lamictal** **Logem**
Tab dispersible 100 mg	**Arrow-Lamotrigine** **Lamictal** **Logem**

Current market overview

In the 2018 financial year, the annual net CPB expenditure on lamotrigine was approximately [redacted]

Overall usage of lamotrigine has increased over the last 10 financial years. Lamictal's (GSK), the innovator product, market share has remained stable over the last five years at approximately (60%) with the two generic brands competing for the remaining market.

Patient dispensing history

As there are multiple brands listed (Lamictal, Arrow-Lamotrigine and Logem), changing brands can and does occur at a pharmacy level unless the prescription has been annotated with the brand and it is specified on the prescription that no brand substitution is allowed.

Our dispensing data shows that of all patients (12,500 patients in total) who received a prescription for lamotrigine in 2018:

- around 50% (6,250) changed brands at least once;
- around 4,000 patients changed brands two or more times; and
- some patients (365) changed brands at least 10 times

The dispensing data is available in further detail in Appendix Six.

RFP process

PHARMAC developed an RFP based on advice from the Neurological and Mental Health Subcommittees of PTAC (November 2015, November 2016 respectively) (full minutes are provided in Appendix Three) The summary of this advice was:

- The Neurological Subcommittee considered it would be appropriate to run a competitive process which would result in only one brand of lamotrigine being listed in the Pharmaceutical Schedule; and

- The Mental Health Subcommittee considered that it would not be clinically problematic to switch patients from one brand to another, although it would require additional work by prescribers and pharmacists to reassure patients who switched brands.

Taking this advice and our previous experience into account we considered that it would be possible and clinically reasonable to implement a change in funded brands

PHARMAC released a Request for Proposals (RFP) for the supply of lamotrigine chewable/dispersible tablets on 14 June 2018. The purpose of the RFP was to obtain the best possible pricing from suppliers to manage costs and to create savings that could be used to fund new investments.

PHARMAC received [redacted] proposals from [redacted] suppliers. An Evaluation Committee made up of PHARMAC staff met on 26 July 2018 and considered all proposals (minutes are available should any Board member wish to review them). No conflicts of interest were declared from any participants in the Committee.

Table 1 summarises the budget impact analysis of the different proposals ranked by estimated savings. [redacted] We carefully considered the benefits and risks of each proposal and noted that, whatever sole supply arrangement was decided on, it would involve at least 40% of the people receiving lamotrigine switching brands. [redacted]

[redacted]

	2019	2020	2021	2022	2023	3 YR NPV	5 YR NPV
[redacted]							

Consultation feedback

A consultation letter was circulated on 29 August 2018 to all suppliers and other parties that, in the view of PHARMAC, may be affected by the recommendations contained in this paper This included: PTAC and its relevant Subcommittees, clinicians and pharmacies involved in the treatment of epilepsy and mental health conditions, Ministry of Health, DHBs, software vendors, Suppliers, interested parties

PHARMAC received 32 responses to the consultation Eight of the responses were from healthcare professionals (HCPs), 17 from consumers, three from suppliers and four from others.

In summary, healthcare professionals were generally supportive of the proposal. Concerns regarding the potential for loss of seizure control or mood destabilisation were raised by consumers, consumer groups and pharmaceutical suppliers

Destabilisation of disease is a commonly raised issue at consultation on brand changes in other disease groups However, due to the nature of the disease groups affected by this proposal (epilepsy and mental health) we have sought extensive clinical advice from our Subcommittees on all of the concerns raised and on implementation activities to support patients through the change

The most substantive response we received was from Medsafe and relates to clinical advice provided by the Neurological Subcommittee For this reason, a summary of the concerns raised by Medsafe is provided separately in the section below the table.

Feedback centred around 4 key themes:

1. Support for the proposal.

2 Continuity of supply

    - Important for paediatric and adult formulations of lamotrigine.

3 Implementation activities to support a brand change

    - Health care professionals and patients need to be supported with information and education throughout a transition

    - There needs to be an alternative funding pathway for consideration of those with epilepsy or other conditions who need to change back to their old brand, or who are not able to change brands

4. Risk of a brand change.
    - Loss of seizure control or mood destabilisation could potentially result in a significant impact on a patient's quality of life.

Themes raised in the responses are summarised in the table below. The individual consultation responses are attached in Appendix Four

Theme	Raised by	PHARMAC comment
Support for the proposal		
Generally supportive	Clinicians, Healthcare Professionals, New Zealand League Against Epilepsy (NZLAE), Royal Australian and New Zealand College of Psychiatrists (RANZCP), Academic (Dr Charon Lessing), New Zealand Transport Agency (NZTA)	Noted
Bioequivalence is likely to be close between the different manufacturers. Any differences in bioequivalence will be less than the rather large steps (usually 25mg) that dose adjustments are made by clinicians Savings can be applied elsewhere in the health system.	Clinician	Noted, this is in line with the clinical advice we have received from the joint Neurological and Mental Health Subcommittee.
Reference provided in support of AED brand switching (Holtkamp & Theodore Epilepsia 2018;59:1273-81.)	Clinician	The joint Neurological and Mental Health Subcommittee considered this reference as part of its review of the literature at its 7 February 2019 meeting.
Change in brand and not a treatment change. While there are some minor differences in pharmacokinetics between brands, these particular ones are not mainstream medications for epilepsy, and any risk from changing would be extremely low.	New Zealand Transport Agency (NZTA)	Noted
There is clear evidence that changing brands does not lead to adverse health outcomes, citing a publication (of which the responder is a co-author) Lessing et al Appl Health Econ Health Policy 2014;12:537-46.	Academic [redacted]	The Neurological Subcommittee considered this reference as part of its review of the literature at its November 2015 meeting and again at the joint Neurological/ Mental Health Subcommittee February 2019 meeting.

Continuity of supply		
Highlighted the importance of maintaining supply of the 2 mg and 5 mg tablets	Clinicians, NZLAE	This proposal would not affect the tab 2 mg and 5 mg presentations of lamotrigine tablets which would remain listed and fully funded.
Teva (Arrow-lamotrigine supplier) indicated that should the proposal be approved, it intends to withdraw supply of its brand of 5 mg tablet (Arrow-lamotrigine).	Teva (Supplier of Arrow-Lamotrigine).	There is currently one brand of 2 mg tablet listed (Lamictal) and two brands of the 5 mg tablet (Lamictal and Teva) listed. These are both supplied in accordance with agreements with GSK and Teva. Given that the GSK brand is also listed we consider the risk of interruption to supply as a result of this proposal to be low.
Highlighted importance of continuity of supply if there is a sole supply arrangement for lamotrigine.	Clinicians, NZLAE	For many essential medicines in New Zealand, only one brand is funded, often following a competitive process. Drawing from the experience of supply security for these other medicines, PHARMAC staff consider that having multiple brands of a product in a market does not improve security of supply When there is one supplier, forecasting is more accurate which helps prevent out-of-stock situations. Further, in exchange for market exclusivity, the supply contracts we have in place require suppliers to agree to rigorous conditions to prevent and manage potential out of stocks. This includes significant stock-holding, frequent stock reporting to PHARMAC and a commitment to source a suitable alternative to prevent a potential out-of stock occurring.
Implementation activities to support a brand change		
Change needs to be managed well at a pharmacy level. Patients need to be supported during the transition	Clinicians, RANZCP, NZLAE, Consumer groups (Epilepsy NZ + Epilepsy Waikato), Consumers	PHARMAC staff have developed a comprehensive implementation plan that includes activities to help ensure that adequate information, education, and reassurance would be provided to healthcare professionals and patients
All epilepsy patients should be given 3-months supply of their medication at once.	NZLAE	We have adjusted our proposal based on this feedback The dispensing frequency of lamotrigine would be adjusted to three-monthly from 1 October 2019
There needs to be an alternative pathway for those who need to switch back to their old brand, or who are not able to change brands	RANZCP, Consumer groups (Epilepsy NZ + Epilepsy Waikato), Consumers	As part of our implementation plan we would develop a specific form for clinicians to use to apply via our exceptional circumstances process for any patients who experience exceptional difficulties with the lamotrigine brand change to remain on their current brand

Risks of a brand change		
People with epilepsy and bipolar disorder are generally averse to change and that previous brand changes for these groups have been challenging.	Pharmacy Guild, Suppliers (GSK Lamictal supplier and Teva, Arrow-lamotrigine supplier), Consumer groups (Epilepsy NZ + Epilepsy Waikato), Consumers	Our implementation plan includes activities to help ensure that adequate information and education would be provided to healthcare professionals and patients
Research shows that brand changes can have flow on effects resulting in increased healthcare costs from hospitalisations and ED admissions (Kjoenniksen et al Pharm World Sci. 2006;28:284-9.)	Pharmacy Guild	The joint Neurological and Mental Health Subcommittee considered this reference as part of its review of the literature at its 7 February 2019 meeting. The clinical advice of relevance that we received from this meeting was, in summary, that there was a significant body of published evidence regarding changing between lamotrigine brands and that the majority of evidence provided by high quality studies 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.
Consider that there is a risk of loss of seizure control when switching brands of AEDs	Suppliers (GSK – Lamictal supplier and Teva, (Arrow-lamotrigine supplier), Consumer groups (Epilepsy NZ + Epilepsy Waikato), Consumers	The clinical advice, in summary, we received from the joint Neurological and Mental Health Subcommittee at its 7 February 2019 meeting is that, based on the available evidence, there is no pharmacological reason to suggest there would be a clinical problem with changing brands of lamotrigine, and that patients experience adverse events, e.g. breakthrough seizures, even when there is no brand change The joint Neurological and Mental Health Subcommittee considered that in the event of a brand change there would be patients who experience adverse events that would attribute these to the change, and that factors likely to contribute to this perception could include reduced adherence, nocebo, or other psychological factors. PHARMAC staff have sought extensive clinical advice and have developed a comprehensive implementation plan to support the brand change and manage potential and perceived clinical risk
Noted the impacts that loss of seizure control can have: loss of licence, loss of employment, mental health issues, burden on health system (Dr visits, hospital admissions, injury), loss of independence, effects on education and learning, effects on family/relationships and death	Consumer groups (Epilepsy NZ + Epilepsy Waikato), Consumers	We acknowledge that epilepsy has a significant impact on quality of life in that activities such as employment, driving and social interaction are dependent on control of the disease; and, that consequences of uncontrolled seizures can be severe (death, severe injury, drowning, drowning inability to drive) The chronic nature of the disease means that people with epilepsy, even on treatment, can have recurrent and spontaneous seizures.

Concerned about the potential for re-occurrence of currently well managed bipolar symptoms, and the potential for increased health care needs as a result Concerns for people who take both venlafaxine and lamotrigine as they have just been through a brand change for venlafaxine and some experienced anxiety and depression as a result.		The clinical advice we have received is that it would be appropriate to move to one funded brand of lamotrigine, with accompanying implementation support PHARMAC staff have sought extensive clinical advice and have developed a comprehensive implementation plan to support the brand change and manage potential and perceived clinical risk
Concerns for changing brands while pregnant	Consumers	The clinical advice we have received is that pregnant patients, and some children, with epilepsy may have difficulty with a brand change depending on their individual circumstances, but that these patients should already be under the care of a specialist who could help them through any brand transition If a pregnant woman was to experience exceptional difficulty with a brand change their clinician could apply via our exceptional circumstances process to remain on their current brand
Other		
A range of procedural concerns, including the fact that PHARMAC has not disclosed the price of Logem at consultation, and insufficient consultation generally	Teva, Arrow-lamotrigine supplier	PHARMAC considers that all necessary aspects of the proposal were included in the consultation to allow for informed feedback e g a proposed brand change and all proposed timeframes for Schedule changes While cost is a matter of some interest to a range of parties, it is primarily a matter for PHARMAC which has sole responsibility for managing the pharmaceutical budget. Pricing detail was not included to avoid the disclosure of commercially sensitive information, thereby leaving alternative bidder options open (and protecting the position of the proposed supplier) in the event that PHARMAC decided not to progress the proposal Pricing would be disclosed in the notification (should the proposal be approved). PHARMAC staff consider that the consultation process carried out has been sufficient in all respects.

Medsafe consultation feedback

The Medsafe consultation response (letter dated 19 September 2018) (attached in Appendix Five) highlighted concerns about switching brands of antiepileptic medicines and about the evidence that was considered by the Neurological Subcommittee in support of this. Medsafe cited references, and updated advice from the UK Medicines & Healthcare products Regulatory Agency (MHRA), not previously considered by the Subcommittee.

PHARMAC staff met with representatives from Medsafe (on 13 November 2018) to better understand the issues raised in its feedback. In summary, we understood the following from this meeting (full details are available in the file note, Appendix Five):

- Medsafe was not supportive of a proposal to move to one funded brand of lamotrigine due to concerns about the potential for patients to experience loss of seizure control as a result of a brand change.
- Medsafe had concerns about the advice, and interpretation of the literature, that was provided by the Neurological Subcommittee at its meeting in November 2015.
- Lamotrigine is not a narrow-therapeutic index medicine.
- All generic brands of lamotrigine approved in New Zealand are considered bioequivalent to the innovator, Lamictal
- Medsafe's feedback relates to switching between any brand of lamotrigine. It is not specific to the innovator brand (Lamictal)
- With the exception of one recent (unpublished) article regarding anti-epileptic brand switching, and the articles provided in Medsafe's consultation feedback, Medsafe was not aware of other important studies of interest that had not been considered by the Neurological Subcommittee.

Following the meeting we received an additional written response from Medsafe to clarify its position regarding potential funding changes for lamotrigine. In a letter (dated 21 November 2018) Medsafe highlighted additional concerns with the literature considered by the Subcommittee and a suggestion that a review of the scientific literature may reveal additional useful information. It also provided the following suggestions for implementation should the proposal go ahead:

- All patients should be reviewed by their GP before switching brands, and counselling should be provided by a GP before the patient gets to their pharmacy (before the patient has their prescription dispensed).
- GPs should refer the most vulnerable patients (those who are seizure free and those with labile seizures) for specialist oversight of a brand switch.
- A patient leaflet, to help explain the changes, should be provided by GPs, specialists and pharmacists.
- All patients should be actively followed up to check they are coping with the change
- An alternative funding mechanism should be made more accessible for patients who need to switch back to their original brand

We replied to Medsafe (email dated 18 December 2018), to clarify several points that were raised in its 21 November letter and also to thank it for the feedback and to let it know that we would be seeking further advice from our clinical advisors (email attached in Appendix Five)

As noted earlier in the paper, given the concerns raised by Medsafe, and others, we then sought further advice from a joint meeting of both the Neurological and Mental Health Subcommittees (referred to below as the Subcommittee) in February 2019.

The Subcommittee noted the concerns highlighted by Medsafe regarding the potential and consequence for loss of seizure control as a result of a brand change for lamotrigine and considered that the Subcommittee had formed its view (of support for the proposal to change brands), based on its own assessment of the literature.

The Subcommittee considered all additional information and feedback provided by Medsafe (and other consultation feedback) and concluded 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 was supportive of the proposal to move to one funded brand of lamotrigine (Logem), with implementation support as discussed below.

PHARMAC staff note that the Logem, and the Arrow Lamotrigine, brand have both been registered by Medsafe to be bioequivalent to the innovator (Lamictal) We note that Medsafe's feedback is predominantly related to pharmacovigilance concerns as opposed to quality or safety concerns with the brand. We note that through meeting with Medsafe, and exchanges of information, Medsafes position has somewhat evolved; however some of its concerns remain. We consider that we have taken sufficient clinical advice from our own clinical advisors on the risks associated with a brand change of lamotrigine; and, based on the Subcommittee's advice, are supportive of the proposal to change to one funded brand of lamotrigine (Logem)

We note that Medsafe provided specific suggestions around implementation should the proposal be approved Our proposed activities are largely in line with these suggestions, with the exception of ensuring that all patients are seen and counselled by their GP before changing brands and that all vulnerable patients (those who are seizure free and those with labile seizures) should be referred for specialist oversight The Subcommittee considered the suggested activities and advised not all were clinically necessary or practical in terms of health sector resource capacity. PHARMAC staff note that we have developed our implementation plan in line with our Subcommittees' advice

Implementation and transition support

Section 49(b) of the Act requires PHARMAC to take measures to inform the public, groups and individuals of PHARMAC's decisions concerning the pharmaceutical schedule. Accordingly, if the recommendations contained in this paper are adopted, PHARMAC staff will take the following measures to inform the public, groups and individuals of that decision. We will:

- Develop a notification and communication plan for this proposed brand change, which will include the sequencing of events around this plan.

- Notify health professionals, suppliers, prescriber and pharmacy IT vendors, consumer organisations and public through a notification letter. This will be sent, with a covering email, directly to representative organisations, and those with whom we consulted It will also be uploaded to the PHARMAC website

Brand changes are part of PHARMAC's core business. PHARMAC has recently managed some difficult brand changes, including the venlafaxine change which drew media attention We are aware that a lamotrigine brand change would likely cause some concern amongst some of our sector colleagues and some patients.

The focus of our implementation approach would include the following key activities:

- maintain open lines of communication and work closely with sector colleagues and other agencies, including Medsafe, Centre for Adverse Reactions Monitoring (CARM) and New Zealand Transport Authority (NZTA) particularly during the transition period of the change;

- provide clear information to health care professionals (in particular prescribers in primary and secondary care and community pharmacists) about the change and activities available to help them support patients during the brand change

- provide patient focussed resources, including website and downloadable information to explain the brand using language that would make the brand change understandable for consumer organisations and patients.

- pay a brand switch fee to community pharmacy in recognition of the additional patient counselling that would be required by pharmacists during the brand change.

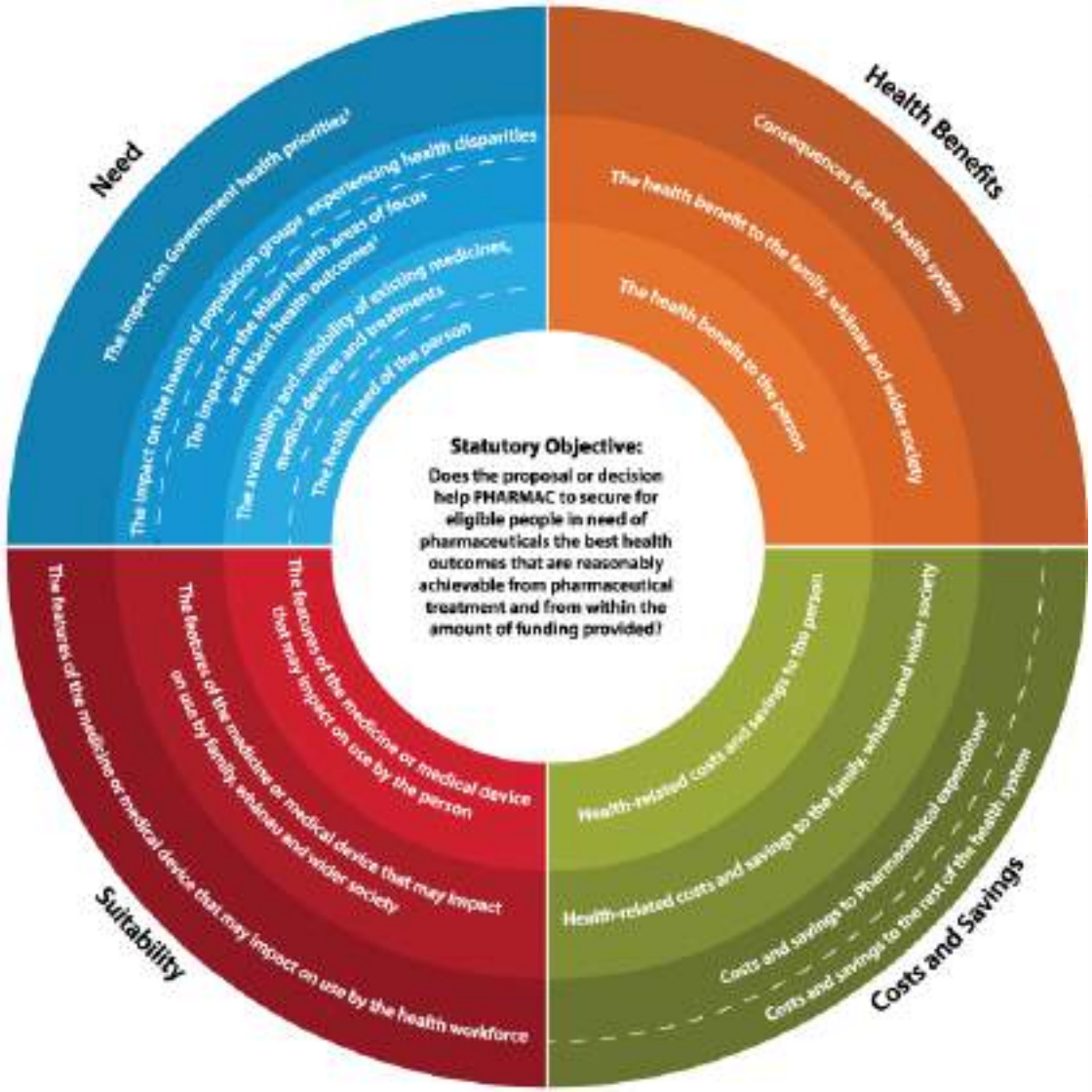
- provide a mechanism to remunerate general practice appointment fees for those patients requiring specific counselling and support with their lamotrigine brand change from their general practitioner; and

- provide a mechanism under the exceptional circumstances framework for prescribers to apply for their patient to remain on their current brand of lamotrigine. This would be for those patients they think would not manage this brand change

Our previous experience, pre-engagement with some stakeholders prior to running a RFP, consultation feedback and advice from the Neurological and Mental Health Subcommittees have contributed to the development of the implementation approach to support this brand change. A comprehensive proposed implementation approach can be found in Appendix Two.

Factors for Consideration

This paper sets out PHARMAC staff's assessment of the proposal using the Factors for Consideration in the Operating Policies and Procedures Some Factors may be more or less relevant (or may not be relevant at all) depending on the type and nature of the decision being made and, therefore, judgement is always required The Board is not bound to accept PHARMAC staff's assessment of the proposal under the Factors for Consideration and may attribute different significance to each of the Factors from that attributed by PHARMAC staff.



Footnotes

[1] The person receiving the medicine or medical device must be an eligible person, as set out in the Health and Disability Services Eligibility Direction 2011 under Section 32 of the New Zealand Public Health and Disability Services Act 2000

[2] The current Māori health areas of focus are set out in PHARMAC's Te Whaioranga Strategy.

[3] Government health priorities are currently communicated to PHARMAC by the Minister of Health's Letter of Expectations.

[4] Pharmaceutical expenditure includes the impact on the Combined Pharmaceutical Budget (CPB) and / or DHB hospital budgets (as appropriate).

[5] Please note PHARMAC's Factors for Consideration schematic currently does not explicitly refer to the health needs of family, whānau and wider society, but this factor should be considered alongside those depicted in the schematic

Factors for Consideration

Health need

Disease/illness

Lamotrigine is indicated in the treatment of epilepsy, for partial seizures and generalised seizures, including tonic-clonic seizures and seizures associated with Lennox Gastaut Syndrome It is also indicated for the prevention of mood episodes in patients with bipolar disorder, predominantly by preventing depressive episodes.

In addition, the clinical advice we have received from our Subcommittees indicates that patients are likely to also be prescribed lamotrigine for behavioural disorders, schizoaffective disorder and a small number of patients could also be taking it for trigeminal neuralgia

Availability and suitability of existing treatments

PHARMAC currently lists and fully funds a number of Anti Epileptic Drugs (AEDs) including sodium valproate, carbamazepine, phenytoin, levetiracetam, gabapentin, pregabalin and topiramate Some of these are also used to treat mental health conditions There is also a large number of antidepressants (e.g. venlafaxine, citalopram, amitriptyline etc) and antipyschotics (e.g. lithium carbonate, olanzapine, aripiprazole etc) listed and fully funded for the treatment of various mental health conditions However, despite the large numbers of other funded treatments for epilepsy and mental health disorders generally, it is unlikely that any of these would be a suitable substitute for lamotrigine without significant impact to patients.

As previously noted, there are currently three brands of lamotrigine listed on the Pharmaceutical Schedule (Lamictal, supplied by GSK; Arrow-Lamotrigine, supplied by Teva; and Logem, supplied by Mylan)

There is currently one brand of 2 mg tablet listed (Lamictal) and two brands of the 5 mg tablet (Lamictal and Teva) listed These are both supplied in accordance with agreements with GSK and Teva. We note that, at consultation, Teva has indicated that should the proposal be approved, it intends to withdraw supply of its brand of 5 mg tablet (Arrow lamotrigine) Given that the GSK brand is also listed we consider the risk of interruption to supply as a result of this proposal to be low. There were 40 patients dispensed the 2 mg lamotrigine tablet and 252 patients dispensed the 5 mg tablet in 2018

Should the proposal be approved, patients living with epilepsy and/or mental health conditions would continue to have access to a fully funded lamotrigine product with the same range of dose strengths as those that are currently funded.

Health need of family, whānau, and wider society

The health needs of primary caregivers and family and whānau of individuals currently receiving treatment with lamotrigine would remain unchanged with this proposal as patients would continue to have access to a fully funded lamotrigine product for the treatment of epilepsy and some mental health conditions.

Impact on the Māori health areas of focus and Māori health outcomes

Mental health is a Māori health area of focus (as outlined in the Te Whaioranga Strategy) According to BPAC (link) bipolar disorder may be more prevalent among Māori (4 6%) compared to people of European and other ethnicities (1.8%).

The Neurological Subcommittee considered, at its November 2016 meeting, that there may be a higher prevalence of epilepsy among Māori compared with the overall population. PHARMAC staff note that no references were cited by the Subcommittee to confirm this We note a retrospective review of adult patients presenting to emergency departments in the Wellington region reported that Māori were overrepresented in the patients presenting with a seizure to hospital (Joshi et al NZMJ 2015;128:30-35), which may support the Subcommittee's considerations.

We consider that this proposal is unlikely to have a significant clinical impact on Māori, as while there may be a higher disease prevalence, all patients would continue to have access to a fully funded brand.

The impact on the health outcomes of population groups experiencing health disparities

We are not aware of any population among the various indications for lamotrigine that would be experiencing health disparities and who might be impacted by this proposal given that this proposal represents a brand change

Is the disease/illness a Government health priority

The Minister of Health's Letter of Expectations 2018/19 (also in PHARMAC's Statement of Intent) outlined that PHARMAC should:

- Manage brand switches and high-profile decisions carefully
- Bear in mind the effect total change management demands on the sector when PHARMAC plans the implementation of individual changes to the Schedule

PHARMAC staff consider that we have given full consideration of potential issues relating to the brand changes of these pharmaceuticals considered in this proposal PHARMAC staff have sought extensive clinical advice and have developed a comprehensive implementation plan to support the brand change. A description of how PHARMAC would plan to manage this brand change is provided in the implementation section of this paper

Health Benefit

Health benefits to the person

This proposal would not amend access criteria for funded lamotrigine. Lamotrigine is currently open listed

Both Logem (Mylan) and Arrow Lamotrigine (Teva) brands of lamotrigine are Medsafe registered and used the innovator brand (one of the currently funded brands), Lamictal, as the reference product; therefore, it is considered that both brands would have the same clinical effect and health benefits/risks. We note that approximately 30% of patients are currently taking the Arrow-Lamotrigine brand and would therefore be switching from one generic

medicine to another (Logem). Medsafe does not consider lamotrigine to be a narrow therapeutic index drug and therefore we consider switching between generic brands of lamotrigine to be no different to any other pharmaceutical brand change

As noted above, we have taken extensive clinical advice on this potential brand change, summarised as follows:

- There is no pharmacological reason to suggest there would be a clinical problem with changing brands of lamotrigine for patients with epilepsy or mental health conditions.

- Patients experience adverse events, e.g. breakthrough seizures, even when there is no brand change In the event of a brand change, it is likely that there would be patients who experience adverse events, and some of those adverse events may be attributed to the change; factors likely to contribute to this perception could include reduced adherence, nocebo effect or other psychological factors

- Based on the literature, there would be seizure recurrence for a proportion of patients (7-22% of patients, over a 2-year period), who are currently seizure free, and on treatment, whether or not there was a change of brands (should the proposal go ahead)

- Pregnant patients, and some children, with epilepsy may have difficulty with a brand change depending on their individual circumstances, but these patients should already be under the care of a specialist who could help them through any brand transition.

- There is likely to be a subset of epilepsy and mental health patients for whom a brand change could be difficult, but that identifying these patients prior to any change would be challenging

- A mechanism would be needed for PHARMAC to consider continued funding of their existing brand for patients with epilepsy or other conditions for whom any lamotrigine brand change may not be appropriate or has not been tolerated The Named Patient Pharmaceutical Assessment (NPPA) pathway could be for this but a specific form for lamotrigine, as opposed to the NPPA form, would be developed to assist applying clinicians with providing the relevant information

- Ensuring sufficient information, education and reassurance to healthcare professionals and patients would be required to support patients with epilepsy or a mental health condition should there be a brand change for lamotrigine.

Our Subcommittees' advice has highlighted that patients with epilepsy and mental health conditions carry a background risk of adverse events, e.g. breakthrough seizures, even when on stable treatment regimens A risk of this proposal is that people taking lamotrigine for epilepsy or mental health conditions may attribute any adverse events that they might experience around the time of the brand change as being caused by the change itself. Any adverse events attributed to a brand change could generate media attention or impact our ability to successfully implement future brand changes.

PHARMAC staff have developed a comprehensive implementation plan to support the lamotrigine brand change (should it be approved) based on the clinical advice we have received, consultation feedback and our experience with other brand changes A description of how PHARMAC staff would plan to manage this brand change is provided in the implementation section of this paper and the full implementation approach in Appendix Two.

In addition, in response to consultation feedback that 3 monthly (stat) dispensing may improve adherence, we are proposing to make changes to the lamotrigine dispensing frequency We note that there is potential for poor adherence regardless of whether or not a pharmaceutical is dispensed stat. We are not aware of any evidence to support increased adherence from stat dispensing (or the reverse from its removal) Lamotrigine is currently able to be dispensed stat if endorsed "certified exemption" by the prescriber We understand from anecdotal reports that this is not widely known and are therefore supportive of the change in dispensing frequency from monthly to three monthly If monthly dispensing was, in practice, a barrier to adherence then the health benefit to the person may be improved.

Health benefit to family and whānau

The health benefit to others would be unchanged as a result of this proposal.

Consequences for the health system

The Neurological and Mental Health Subcommittees advised that there is no reason to recommend routine checks of lamotrigine serum levels if a brand change was to occur.

Based on the clinical advice we have received the majority of patients, with appropriate implementation support, should not experience a clinical problem with a brand change of lamotrigine It is likely that a small number of patients may require additional assistance, for example an extra visit to their GP, or a referral to a Neurologist if they are experiencing exceptional difficulty. Our implementation plan outlines the support we plan to provide to clinicians for any patients experiencing exceptional difficulty

Clinical advice

As noted earlier, there has been considerable historical resistance expressed by physicians to changes in the antiepileptic medicines market. However, more recent clinical studies and international recommendations for brand changes in this market have provided further evidence to support these activities and the clinical advice we have received has evolved as a result. PHARMAC staff have responded accordingly and continue to seek updated advice. The clinical advice we have received has informed successful brand changes for two other antiepileptic medicines in New Zealand: levetiracetam and gabapentin. However, this would be the first time that PHARMAC has run a sole supply competitive process in a well established antiepileptic market For this reason, we have sought extensive clinical advice PTAC and relevant Subcommittees have provided clinical advice at various stages.

Below is a list of relevant clinical advice received after introduction of generic lamotrigine All relevant minutes are provided in Appendix Three.

- **19 April 2007** Neurological Subcommittee meeting minutes.
- **2 April 2009** Neurological Subcommittee meeting minutes
- **5 August 2010** Neurological Subcommittee meeting minutes.
- **24 July 2012** Neurological Subcommittee meeting minutes

In summary the Subcommittee considered:

- that patients stabilised on one brand of lamotrigine should not switch brands;
- the consequences of reduced therapeutic benefit in patients with epilepsy were substantial compared to other disorders (e g Not allowed to drive for 12 months following a seizure);
- insufficient evidence had been reviewed to establish the safety of brand switching for patients with epilepsy;
- there are potentially greater risks associated with switching between generic products compared with switching between the innovator brand and a generic; and

2 August 2013 PTAC meeting minutes*, review of proposal for generic sole supply for sodium valproate (*web minutes).

Summarised main relevant points:

- It was Medsafe's role to consider and determine issues related to bioequivalence, that there is a difference between 'bioequivalence' and 'interchangeability', and that the highest levels of evidence indicate that there should not be a problem with generic substitution.
- In one study[1], lamotrigine or divalproex brand to generic switching was not associated with increased incidence of events or utilisation changes compared with patients remaining on the branded product
- That recent discussion related to another AED indicates concerns from neurologists about changing brands of AED due to the risk of breakthrough seizures and that they would be opposed to compulsory brand switching.
- It may be difficult to convince patients of the safety of changing brands Members considered that the possible anxiety related to switching might cause seizures.

11 November 2015 Neurological Subcommittee meeting minutes (web minutes)

Summarised main relevant points:

- 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.
- A retrospective cohort study[1] involving 616 patients, reported there was no statistically significant increase in emergency department visits, hospitalisations or condition specific encounters for patients with epilepsy, bipolar or migraine who switched brands of lamotrigine

- Another study[2] in the New Zealand context also reported no differences in health outcomes measures (hospital admissions, use of specialist service, death, use of other AEDs, adverse reports) were associated with switching from originator lamotrigine to a generic equivalent compared with those who did not switch brands

- The Subcommittee considered that a managed switch to one brand of lamotrigine would be preferable to having multiple brands listed.

- The Subcommittee considered a competitive process for one brand (sole supply) of lamotrigine would be appropriate, provided that a suitable transition period was available

7 November 2016 Neurological Subcommittee meeting minutes (web minutes)

Summarised main points:

- The Subcommittee considered that it could not perceive a problem with having different suppliers for the adult strength [25, 500 and 100 mg] and the paediatric strength [2 and 5 mg] preparations of lamotrigine tablets.

- Commercial process for lamotrigine may enable supplier perceptions to change about AED markets, incentivising competition for other AED markets.

23 November 2016 Mental Health Subcommittee meeting minutes.

Summarised main points:

- The Subcommittee considered that it would not be clinically problematic from a to switch patients from one brand of lamotrigine to another if necessary (ie no more or less problematic than any other mood stabiliser brand change).

7 February 2019 the Mental Health and Neurological subcommittees jointly considered a paper from PHARMAC staff seeking advice regarding a proposal to move to one funded brand of lamotrigine (Logem) in light of concerns raised during the consultation, in August 2018, on the proposal to move to one funded brand of lamotrigine (Logem) (full minutes are provided in Appendix Three). Note that for convenience the joint meeting of the two Subcommittees are referred to below and, in the minutes, as "the Subcommittee"

Summarised main points:

- The Subcommittee considered all of the consultation feedback, including the concerns raised by Medsafe with regards to the possibility of an increase in breakthrough seizures attributable to a brand change, and considered that based on a full review of the available evidence, there was no pharmacological reason to suggest there would be a clinical problem with changing brands of lamotrigine for patients with epilepsy or mental health conditions

- The Subcommittee noted the concerns highlighted by Medsafe regarding the potential and consequence for loss of seizure control as a result of a brand change for lamotrigine and considered that the Subcommittee had formed its view (of support for the proposal to change brands), based on its own assessment of the literature.

- The Subcommittee considered that there would be patients who experience adverse events, e g breakthrough seizures, even when there is no brand change The Subcommittee considered that, in the event of a brand change, there would be patients who experience adverse events who would attribute these to a brand change, and that factors likely to contribute to this perception could include reduced adherence, nocebo, or other psychological factors.

- The Subcommittee considered that ensuring adequate information, education, and reassurance to healthcare professionals and patients would be required to support patients with epilepsy or a mental health condition should there be a brand change for lamotrigine

- The Subcommittee considered that it was supportive of the proposal to move to one funded brand of lamotrigine (Logem), with implementation support as discussed above

Advisor Conflicts of Interest

The recommendations in this paper relay on advice from the Mental Health and Neurology Subcommittees of PTAC PHARMAC staff note that no conflicts of interest were identified by members of the subcommittees in relation to lamotrigine.

Member (Committee)	**Interest**	**Date of declaration (action taken if recorded)**
Dr Jim Lello (Neurological Subcommittee)	Received some sponsorship from GSK to attend the European Respiratory Society conference in Munich	August 2014
	Attended overseas meetings with partial support from Astra Zeneca and GSK, both of whom have CNS products in NZ	November 2016
Dr Ernest Willoughby (Neurological Subcommittee)	Has been a principal investigator for trials of Multiple Sclerosis treatments for Teva	September 2013
Dr David Menkes (Mental Health Subcommittee)	Was an unpaid co investigator for clozapine bioequivalence studies in 2011 for Douglas Pharmaceuticals, and has published in this area	June 2015
Dr Ian Rosemergy (Neurological Subcommittee)	Received UCB sponsorship to attend a UCB epilepsy meeting in Melbourne Australia in March 2012	July 2012
	Attended an Epilepsy meeting in Auckland sponsored by BioCSL in September 2015	November 2015
	Received sponsorship from Sanofi to attend the European Epilepsy meeting in August 2018. Sponsorship was in the form of covering costs of the registration fee	July 2018 (Full participation was permitted under the Boards Standing Permission)

Suitability

This proposal would not impact the availability of current treatments with the full range of presentations continuing to be funded via the Pharmaceutical Schedule Although there would be some changes to the status of particular brands, two currently funded brands would be delisted, PHARMAC staff do not consider these changes would impact the availability or suitability of existing treatments for patients

Logem is a similar shape, size and colour to the market leading product and also has the same flavour. There would be no change to the range of strengths or formulations.

Costs and Savings

Health related costs and savings to the person; and to the family, whānau and wider community.

The costs to patients currently receiving lamotrigine would be largely unchanged if they change to the funded brand, Logem. A small proportion of patients may experience an increased cost if they require additional visits to their clinician in order to be supported through the proposed switch As part of our implementation activities PHARMAC would cover primary care appointment co-payment fees for those patients requiring extra specific support with their lamotrigine brand change.

The proposed change in dispensing frequency from monthly to three-monthly may result in increased convenience and decreased travel costs for some patients.

Cost and savings to Pharmaceutical expenditure

The proposal would result in significant savings to the Combined Pharmaceutical Budget of approximately [redacted] over 5 years (NPV, 8% discount).

It is estimated that the proposal would provide a small amount of savings in the 2018/19 financial year of [redacted] from the reduced cost of the Logem brand for existing patients We estimate the following level of savings over the next 5 Years:

FYR	2019	2020	2021	2022	2023	5-year NPV
Savings to the CPB	[redacted]	[redacted] m	[redacted] m	[redacted] m	[redacted] m	[redacted]

PHARMAC staff considered a counterfactual to this sole supply proposal, namely allowing patients to stay on their current brand of lamotrigine ('grand-parent') and requiring any new patients (from a particular date) to use one specific brand of lamotrigine. This would require PHARMAC to re-run a commercial process as we would be offering a significantly smaller market to any potential 'sole' supplier for new patients The savings from this counterfactual option would be significantly lower than the savings that would be generated from having one supplier in the market.

PHARMAC staff have analysed two scenarios using this counterfactual, the first is a "best case scenario" in that it is assumed that, following a new commercial process, GSK is the successful bidder offering a [redacted] on its current list price. Under this scenario estimated savings would be around [redacted] (5 year NPV)

The second scenario assumes a likely more realistic [redacted] discount on [redacted] under which estimated savings would be around [redacted] (5-year NPV)

If the above approach was taken [redacted]

On balance, given the supportive clinical advice we have received, the opportunity for large savings in this market and possibility for other AED markets in the future, we consider the proposal for sole supply of lamotrigine to be the preferred option

Costs and savings to the rest of the health system

We would be paying a Brand Switch Fee to pharmacists to reimburse them for their time supporting this brand change, including time spent providing education and information to patients.

As noted above and as part of our implementation activities PHARMAC plans to cover extra general practitioner appointment co-payment fees for those patients identified as requiring specific support with their lamotrigine brand change We anticipate, based on the clinical advice received, that this would be for a small number of patients.

If this proposal is approved there would also be an overall savings to DHBs of [redacted] annum as a result of changing the frequency of dispensing for lamotrigine from monthly (non stat) to three-monthly (stat)

There would also be a reduction in pharmacy mark-up. The mark up is calculated as a percentage of the list price, so when list prices fall, so does the mark up We forecast this would save DHBs around [redacted] per year.

Cost Effectiveness

The cost effectiveness of lamotrigine would be improved by the proposal as it would provide the same funded access at a lower cost

Legal Advice

[redacted]

Legal Advisors' View

Confidential and Privileged Advice from PHARMAC's General Counsel

[redacted]

Appendices

Appendix One:	Pharmaceutical Schedule resolutions.
Appendix Two:	Implementation plan
Appendix Three:	Relevant Neurological and Mental Health Subcommittee minutes.
Appendix Four:	Consultation letter and Consultation Responses.
Appendix Five:	Medsafe correspondence
Appendix Six:	Lamotrigine dispensing data.