Jane Wright

From: Charon Lessing <[redacted]
Sent: Thursday, 6 September 2018 4:54 PM
To: Procurement
Subject: lamotrigine consultation
Attachments: lamot_published.pdf

I would like to support the proposal to fund a single brand of lamotrigine. This is based on clear evidence that changing brands does not lead to adverse health outcomes - as determined in my doctoral research into this specific medicine brand switch in the NZ setting.

A summary of the findings from 1,655 adult NZ patients analysed over 12 months post- brand switch include:

- Approximately one-quarter of all patients using the originator brand of lamotrigine switched to generic lamotrigine, half of whom made the switch within 60 days of the policy implementation (2007).
- **Multiple switches (three or more) between generic and brand products were evident** for around 10 % of switchers.
- Switch-back rates of 3 % were apparent within 30 days post-switch.
- **No difference in heath outcome measures** was associated with switching from originator lamotrigine to a generic equivalent.

The published article is attached.

Sincerely
Dr Charon Lessing

From: [redacted]
Sent: Thursday, 30 August 2018 9:08 p.m.
To: Procurement
Cc: '[redacted]
Subject: [SPAM]? feedback on change to lamotrogine/ Lamictal medication

Follow Up Flag: Follow up
Flag Status: Flagged

Categories: Tim

Kia ora,

My [redacted] old daughter is currently on Lamictal to treat her epilepsy. She has had this medication since she was [redacted] old and she currently has 100mg daily. I am nervous about the changing of brands and would like to request that the funding is not based on amount of mg necessarily but also for the age of the person taking it. As a young and fragile girl she may respond badly to changing brands and I note that you have mentioned not changing the amount for young children taking less.

I will contact her paediatrician and neurologist at starship for clarification on what the potential impacts would be on [redacted] should she have to change brands.

I would also like to know how much of a cost it would be (can you guess? You'd have a better idea that I would) so that I can anticipate this cost in our future.

Nga mihi

[redacted]

To: [redacted]
From: [redacted]
Sent: Thur 30/08/2018 9:33:40 a.m
Importance: Normal
Subject: [SPAM]? Submission on proposal to move to one funded brand of lamotrigine
MAIL_RECEIVED: Thur 30/08/2018 9:34:33 a.m

To whom it may concern

I wish to submit in opposition to the proposed move to a single funded brand of lamotrigine (Logem).

The reasons for my opposition are as follows:
The American Academy of Neurology published a position statement opposing “generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician’s approval,” noting that minor differences between generic and branded products may result in breakthrough seizures and/or toxicity. (Liow K, Barkley GL, Pollard JR, Harden CL, Bazil CW. Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy. Neurology. 2007;68:1249-1250).

As such, the appropriateness of generic substitution for a given patient should be evaluated on a case-by-case basis. Given the serious adverse health effects associated with uncontrolled epilepsy, a lack of access to a more appropriate form of lamotrigine for financial reasons and/or because pharmacies will no longer stock the alternative is completely inequitable and unacceptable.

On a personal note, my [redacted]old daughter has epilepsy. Lamictal is one of her medications. She has tried a number of different anti-epileptic medications and experienced adverse side effects or lack of efficacy from most she has tried. I do not wish to experiment with an alternative form of lamotrigine based on her adverse reactions to other medications she has tried. I do not consider it fair or equitable that if this proposal goes ahead we will have to pay more to keep her on this medication, or be unable to source it should pharmacies no longer supply it.

Neurology is complex and the choice of appropriate medication including brand formulation should be given to appropriately experienced and qualified neurologists. Please do not take that choice away, especially for those of us who rely on the current formulation.

Thank you for your consideration of my submission. In summary I oppose the proposal and seek that it not proceed.

Kind regards

[redacted]

Sent from my iPhone

To: [redacted]
From: [redacted]
Sent: Wed 5/09/2018 9:13:04 p.m
Importance: Normal
Subject: [SPAM]? Lamotrogine changes
MAIL_RECEIVED: Wed 5/09/2018 9:14:01 p.m

Hi,
I am writing to discourage the proposal to stop funding Lamictal brand of Lamotrogine. I have epilepsy and currently take 250mg a day. I have tried the other brands but they have given me bad side effects such as severe headaches. On top of that, the change over period will be when I am [redacted] and the drs have said this is the safest to be on and also it would be [redacted]

Please do not accept this proposal to stop funding the important medication that I take every day!

Kind regards,
[redacted]

[redacted]

From: [redacted]
Sent: Thursday, 13 September 2018 12:53 p.m.
To: Procurement
Subject: [SPAM]? Lamictal Submission

Lamictal Lamotrogine for seizures is not like a Paracetamol for headaches and colds.
Comparative scientific analysis of Lamictal and proposed brand should be rigorous to remove any risk of seizures from variation in ingredients.
It is taken in specifically prescribed quantities and when changing from one drug like Dilantin to another like Lamotrogine it is done gradually over 6 months.
I am a nocturnal epileptic but when I miss medication in the morning can have seizures in the evening while still awake. This illustrates that it is very precisely balanced.
If you change brands it must be precisely the same level of Lamotrigine per tablet and a very similar filler to avoid seizures because of a change to the medication while driving etc.

Regards

[redacted]

To: [redacted]
From: [redacted]
Sent: Tue 18/09/2018 8:27:17 a.m
Importance: Normal
Subject: [SPAM]? Lamotrigine change
MAIL_RECEIVED: Tue 18/09/2018 8:27:47 a.m

To whom it may concern,

I have just read of your plans to change this medication to the one brand.

My heart has just sunk.

I have always had the upmost faith in Pharmac and trusted it without question. I have had medication changed before (to generic subsidised versions) without a hitch.

Until effexor was changed.

At the beginning of this year I started to feel very unwell again. My thoughts were turning to suicide and the life that I was living went back down that dark hole of depression.

It took me a little while to work out what the change had been and guess what - the only difference was my medication.

I know that depression / bi polar comes in ups and downs and that is to be expected but the way I went down was so out of the norm.If there are others like me, I am sure that there will be deaths owing to the change in meds and the resistance from Pharmac to even look into it. .

Now, I face the horror of another change. I literally feel nauseous having just read about this.

I know that you do your best to balance out the budget and make the best decisions you can for the health of the population. But, these they are not right for everyone (and I realise they never will be 100%). I am unable to afford paying for effexor. Instead the NZ tax payer is paying for urgent appointments at the mental health unit and with my GP.

If you must go down this route, I beg that you consider those of us who are dealing with the side effects of these actions. Please at least give our GPs an option to allow us to continue with effexor and then lamotrigine at a more reasonable price (for the 5 x 75mg of 'Effexor I take daily it is $35 nper month. Which I do not have.).

This has put me in such a bind - I am unable to work as many hours due to depression and therefore can not afford the price increase for a medication that I know works. I worry that it'll be this times 2 should you look at the lamotrigine as well.

, I really do appreciate how hard you all have to work to make things work but people will die. Physically healthy people who were once stable mentally as well..

Kind regards

[redacted]

From: [redacted]
Sent: Thursday, 20 September 2018 12:51 p.m.
To: Procurement
Subject: [SPAM]? Proposal to move to one funded brand of lamotrigine (Logem)

Follow Up Flag: Follow up
Flag Status: Flagged

Categories: Tim

Do you guys know how hard it can be to achieve success with seizure management in Epilepsy?

It only takes a small change in the persons with Epilepsy regime to go back to square one, and start again to achieve a seizure free life.
People with epilepsy work hard to achieve a seizure free state.
It only takes a small change to disrupt this.

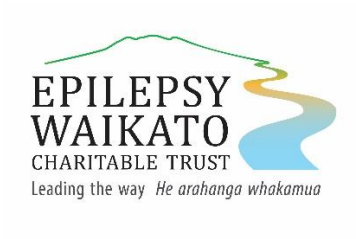
We take this very seriously, as it has big implications.
My [redacted]-old daughter has to manage the following in order to avoid a seizure.
Early nights, strict time taking management of medication, avoiding alcohol, avoiding stress, no clubbing, avoiding flashing lights.
Do you know how hard this has been in her teens and young adult life!!
It only takes a small change in her personal management to trigger a seizure.

When seizure management is not achieved, this affects the possibility of independence with driving (waiting yet another year to get a driver's licence).
It affects work options, calling in sick too often is not good for both the person and the employer.
It may mean another visit by the ambulance, or trip to the hospital.
For some it means broken bones/ teeth with the fall from a seizure.

So, to have finally achieved some success on the current medication (Lamotrogine supplied by Arrow-Lamotrogine), we are in no mood to add another risk by changing brand.
We have vigilantly requested the same brand for the [redacted] my daughter has been diagnosed with Epilepsy.
We believe changing brands may put her at risk of more seizures.
In a community which talks to each other, we hear of other people for whom changing brands have triggered seizures.

Please give us the choice, so we can manage our own medical conditions.
Our Doctors and us know our medical condition best.

Thank you for considering my input.
[redacted]



24 September 2018

Lisa Williams,
Director of Operations
C/- [redacted]
PHARMAC

Dear Lisa,

Re: Feedback to PHARMAC on a proposed change to the funding of lamotrigine dispersible tablets used in the treatment of epilepsy and/or bipolar disorder

The Epilepsy Waikato Charitable Trust (EWCT) is concerned that PHARMAC wishes to

• reduce the funded brands of lamotrigine 25 mg, 50 mg and 100 mg dispersible tablets to just one funded brand (Logem)

• make Logem the only funded brand of 25 mg, 50 mg and 100 mg dispersible tablets in both the community and hospital settings.

As you may appreciate, epilepsy is a complex neurological condition that is mostly managed by anti-epileptic drugs (AEDs). The sole aim of this treatment is to reduce seizures. Once long-term remission has been achieved it then becomes important to avoid even a single break-through seizure subsequently. The social, emotional and financial burden to a person enduring a break-through seizure is immense and such people are then more at risk of a seizure-related death either with status epilepticus or SUDEP. It is therefore incomprehensible that PHARMAC would entertain changing a branded anti-epileptic medication with a generic brand when there is more risk in 'switching' medications for people with epilepsy, who hold on tightly to their established medication regimes, than with any other medical condition.

Establishing seizure control can be a heartache for people with epilepsy. It can take months, even years, to get the medications just right. Quite often a number of AEDs have to be tried at various doses to identify which treatment is most effective and tolerable. Neurologists always aim for monotherapy but, more often than not, additional AEDs are used as adjunctive therapy (always with titration according to therapeutic responses) to get full seizure-control. Multiple AEDs added to the daily regime of seizure treatment increase the potential risk of side effects, and using a generic brand has the potential to differ in its therapeutic response even though it is defined as bioequivalent to the branded one.

Bioequivalent studies are usually carried out with single doses on small numbers of healthy volunteers, who are not receiving other therapies, to eliminate factors that cause variations

in results. PHARMAC staff would likely be aware of such bioequivalent studies when choosing Logem over lamotrigine. However, it is well known that each person with epilepsy will respond to AEDs differently. **We would therefore strongly recommend that PHARMAC uses caution, and cancels this proposal, because of the very significant risk to ~10,000 vulnerable people currently taking lamotrigine**. Some queries to consider with regard to the proposed switch are as follows:

- What if there are serious consequences to any person with epilepsy in that 'switch"?
- What about the potential for breakthrough seizures resulting in a loss of a driver's licence, job, self-esteem, depression or suicide?
- What if neurologists become so tied up in complex management regimes in order to control seizure on each of their clients?
- What if some people have 'brittle' epilepsy and simply cannot tolerate generic medications?
- Will the savings made from generic prescribing of AEDs outweigh the cost of adverse consequences in some patients?

There is a human cost to PHARMAC's proposal and people with epilepsy, already disadvantaged in the community, stand to suffer further, including some potentially fatally, as a result of taking a generic brand of medication that may, or may not, produce a satisfactory cost-saving result to the government. Epilepsy is a complex neural pathway condition largely treated with medications, and a medication 'switch' may just be the undoing of many people with epilepsy tenuously holding onto their lives.

Yours faithfully

[redacted]
Epilepsy advisor
Epilepsy Waikato Charitable Trust (EWCT)
P.O. Box 633
Hamilton 3240
Web: www.ewct.org.nz
[redacted]
[redacted]

To: [redacted]
From: [redacted]
Sent: Sun 23/09/2018 10:10:36 p.m
Importance: Normal
Subject: Change of Lamotrigine to Logem
MAIL_RECEIVED: Sun 23/09/2018 10:11:30 p.m

Dear Sir/ Madam

My name is [redacted] and I am an epileptic taking the 50mg and 100mg of the Lamotrigine. I am a [redacted]r old girl and it has taken me six years to finally find the right dose of medication. Now you are proposing to change the brand of the Lamotrigine to Logem, I was wondering if the change of brand would affect the recipe of the medication, because I cannot take this risk of taking a different recipe as I am almost a year seizure free and able to get my license as of the first of January next year. So if you could let me know if there will be any changes to the recipe that would be much appreciated.

Kind Regards
[redacted]

From: [redacted]
Sent: Monday, 24 September 2018 7:22 p.m.
To: Procurement
Subject: [SPAM]? Submission re lamotrigine brand funding

Hello,

I've just found out by total chance of your proposal about changes to lamotrigine suppliers and as someone who will be affected the most should this go through, ie someone who takes it for epilepsy, I'd like to comment, and also express my concern that you obviously haven't tried very hard to reach the people who take this drug, which wouldn't have been very difficult.

I have been taking Lamictal brand for [redacted], since before the generics were available in NZ. When they did turn up I remember there was some arrangement with Pharmac that those of us already established on Lamictal could continue taking it fully funded as the consequences of switching brands of anti-epileptic drugs was well known by then. You might recall some serious problems that happened when Tegratol was switched a few years earlier. As much as your "experts" will go on about the bioequivalence being the same whatever the brand, you know full well that is not the case in reality because brand switches (of all types of drugs) have a long and clinically proven track record of affecting people individually and there is no guarantee that it won't.

In the case of epilepsy, the consequences of even subtle changes of drug level changes/way the drug metabolises are massive, and even potentially fatal, especially if they have tonic clonic seizures. Can you 100% guarantee that someone fully controlled on one of the brands you propose defunding/making unavailable will stay 100% controlled after switching brands? Will you be responsible for them losing their drivers licence, their job? Can you guarantee that someone with intractable tonic clonics taking Lamictal brand (my situation) isn't going to end up worse?

There are also people incredibly hypersensitive to drug doses. I will cite you my experience as an example. Lamictal is the only AED I have ever been able to take a full adult dose of without going toxic, but it took me 10 years to get up to the 350mgs I'm on. I'm currently in the process of increasing 50mgs- by 5mgs a month. That's how sensitive I am. Can you tell me for certain that switching to another brand of lamotrigine is not going to give me side effects, or even new ones that I don't have now? I've been through forced drug switches in the past (not AEDs) because of Pharmac changes, and I've had serious reactions to them. One was so bad that I'm still paying the full price to continue with the brand, and hoping like hell the drug company doesn't pull it from NZ which happens a lot. My biggest fear has always been GSK pulling Lamictal out; I didn't think it would be Pharmac doing the pulling out.

And on the subject of part/full charges for remaining on our current brands, that's if the drug company decides to even stay in the market here (can you guarantee they will?) The majority of people taking these drugs are on a benefit or low wage so we just can't afford part charges on our meds, and no, the token gesture from WINZ doesn't even come close because that goes into the rent and other bills first. I would be too terrified to take another brand of lamotrigine due to previous experiences- if I had to pay for it then that's my food budget slashed back even more. And I wouldn't be the only one in that situation.

I don't pretend to fully understand the economics behind all of this but I've got a pretty good idea of cost/benefit, and if you put people in a situation where changing a drug that's kept them either seizure free and gainfully employed and that control is lost, well you can work out what that cost will be to the taxpayer, and I'm pretty sure it'll be more than what you save. And for someone in my situation, I'm not exaggerating that even small increases in a lot of the AEDs have put me in hospital toxic, which I'm sure costs an awful

lot. So between the possibility of that happening, never mind the opposite risk of my seizures getting worse- also requiring hospital admissions- maintaining the status quo for all of us is not only the moral and ethical thing to do, but the clinically appropriate, and cost effective in the long run.

I'd like to add that I have absolutely no problem at all with generic drugs, and I fully support their use when it's reasonable. But there is so much published evidence out there about the dangers of switching anti-epileptic drug brands (which I know you are well aware of) and so I submit to you this is not a good idea at all and sincerely hope you will reconsider.

Sincerely

[redacted]

To: [redacted]
From: [redacted]
Sent: Mon 24/09/2018 9:06:48 p.m
Importance: Normal
Subject: Lamotrigine proposal submission
MAIL_RECEIVED: Mon 24/09/2018 9:07:24 p.m
Lamotrigine proposal.pdf

To Whom it May Concern,

Please find my short submission regarding the proposal to move to one funded brand of lamotrigine (Logem).

Kind regards,
[redacted]

[redacted]

24 September 2018

Attn: procurement@pharmac.govt.nz

To Whom It May Concern,

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

As a woman who has epilepsy herself, but also a mother to a teenager with epilepsy I am writing to you with lived experience.

Have you ever experienced having to watch your child 24 hours, 7 days a week due to the fact that they are having adverse reactions to an antiepileptic medicine, which is resulting in them wanting to commit suicide? I have and it is not something that I ever wish to experience again.

Being seizure free and not having severe adverse reactions to an antiepileptic medicine is where we are now living with our daughter. By restricting her choice of medicine, you are not only stripping her of her Health and Disability Consumer Rights, but you are putting her life in jeopardy. If this is down to a cost issue, which it seems to be, how much money do you put on a human life?

We would not be in a unique situation here, therefore I suggest that you keep lamotrigine (Lamictal) as an option for people who are on this medicine.

Kind regards,

[redacted]

From: [redacted]
Sent: Tuesday, 25 September 2018 5:19 p.m.
To: Procurement
Subject: [SPAM]? Feedback re Pharmac proposal to move to one version of lamotrigine

[redacted]

20 September 2018

To Pharmac Decision Makers

Re Proposed Change of Funding for Lamotrigine (Lamictal, Arrow-Lamotrogine, Logem) to single funded brand (Logem)

I am writing as an extremely concerned parent of an [redacted] daughter ([redacted]) who suffers epilepsy (complex partial seizures), and has been using Lamictal since 2012 as part of her treatment programme.

Our family lives were changed forever when our (then [redacted] old) daughter started suffering complex partial seizures. The relief of a diagnosis is then tempered with what has become a long and arduous journey to find a magic "potion" that would successfully treat her condition and allow her to lead a normal life that we all strive to give our children. To this day, we have yet to find the magic potion(s), dosages that will give our now [redacted] old daughter a seizure free life.

Our daughter suffers approximately 10-20 seizures a year. I keep a detailed seizure diary, which lists every date, time, activity, general wellbeing, any possible triggers etc when she has a seizure. She religiously takes her medication every day at 7am and 7pm. Unfortunately, despite the details in the seizure diary, we have been unable to determine any definitive patterns or triggers and rely heavily on the medications prescribed to keep the epilepsy under control.

[redacted] is an academic student and is now studying at [redacted]. We try to enable her to have a normal lifestyle, however her epilepsy places restrictions on her that few of her peers face. As a result, she is currently undergoing counselling to manage expectations. She is currently unable to obtain a driver's licence. She maintains an extremely healthy lifestyle (no drinking, no late nights). We deliberately do not

make any long-haul travel plans, specifically to minimise effect of sleep deprivation. If epilepsy were not a factor in her life, she would be studying Marine Biology. We discussed and decided that it was not realistic for her to have a career in an environment where water is such a crucial part of daily life, however this same environment would put her (and others) in a continued high risk situation. Her dream plans are curtailed, she is working within her current restrictions. We are ever hopeful that we will get to a perfect plan in future. In the meantime, every day is filled with fear that she may have an epileptic event, despite our attempts that we do everything "right" to the best of our abilities.

[redacted] has been under the care of A[redacted] and is now looked after by Dr P[redacted] Despite 3 different neurologists involved in her care, all 3 neurologists have kept one medication constant in her treatment – lamotrigine (specifically, Lamictal). We have tried a range of different medications (Keppra, Topomax, Epilim, Tegretol) as well as Lamictal, but as yet, are not completely seizure-free.

With every changing anti-seizure medication, and especially with Lamictal, we have had a long, protracted titration schedule, to minimise side effects and reduce the risk of drug induced seizures. When first prescribed Lamictal, our regular pharmacist ([redacted]) made it very clear that if we ever changed pharmacies that we should always continue on the same brand (ie Lamictal) of anti-seizure medication to prevent complications. He strongly indicated that as the effect of these medications are so specific, that tiny differences can make these vulnerable patients, even more so. He has never made this comment about any other medications (anti-seizure or otherwise) that we have been prescribed.

Lamictal is such a specific drug, with very clear guidelines with regards to how/when it should be taken. The long titration and no sudden withdrawals are specifically there as protection to minimise side effects and minimise the risk of seizure. This is so different to more generalised medications where generic substitutes are regularly replaced with minimal effects. We have personally experienced this withdrawal of Lamictal – In July 2016, [redacted] underwent VEEG (Video EEG Monitoring) at [redacted], and her medication was withdrawn (under medical supervision at Auckland Hospital) whilst undergoing this. Rather than suffering her "usual" complex partial seizures, [redacted] suffered the far more serious tonic-clonic seizures. This is an absolutely horrifying experience of anyone to witness, and it was due to the withdrawal of her medication – a clear indication of how dangerous any withdrawal is, and how vulnerable our daughter is, to a change in treatment plan.

In our experience, the treatment of epilepsy is "an art, not a science". So many epileptic individuals have so many different treatment plans, showing how sensitive this treatment can be to each individual. Not only do you need to select the "right" drug, but the "right" dosage, at the "right" time (eg hormonal), and combinations.

As a parent you always want the best options for your child - if you remove Lamictal, then you are removing this as an option in our arsenal of treatment plans. You are un-doing the last 6 years of our treatment plan. I am extremely worried that if the generic version of lamotrigine does not work for [redacted], then we have no fallback plan if Lamictal is no longer available.

Please do not remove the one constant medication, that 3 different neurologists have all independently considered to be an essential part of her treatment programme. I do not want my daughter to be placed in a vulnerable situation where she is at risk of a serious seizure, and potentially death, just because some decision maker has decided to remove an option.

Yours sincerely

[redacted]

[redacted]

From: CEO <[redacted]>
Sent: Wednesday, 26 September 2018 1:10 p.m.
To: Procurement
Subject: Submission
Attachments: Pharmac - Lamotrigine.docx

Follow Up Flag: Follow up
Flag Status: Flagged

Please find attached.

Graeme Ambler
CEO

Epilepsy Association of New Zealand Inc
6 Vialou St., PO Box 1074, Hamilton 3240
[redacted]
Email: [redacted] | Website: www.epilepsy.org.nz

Help Line: 0800 EPILEPSY (374 537)

EPILEPSY ASSOCIATION OF NEW ZEALAND INC.
6 Vialou St.,
PO Box 1074
Hamilton 3240, New Zealand

Tel: (07) 834 3556
Email: national@epilepsy.org.nz
Website: www.epilepsy.org.nz
Registered Charity: CC10611

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kia titiro ki te tangata - see the person

26th September 2018

Pharmac
PO Box 10254
WELLINGTON

Email: procurement@pharmac.govt.nz

Submission and Proposal to fund sole supply of Lamotrigine.

Epilepsy Association of New Zealand Inc (Epilepsy New Zealand) appreciates the opportunity to comment on the proposal for Pharmac to move to a one funded brand of Lamotrigine (Logem).

Epilepsy New Zealand is committed to supporting people living with epilepsy so as to positively influence their quality of life.

Notwithstanding comments here, Epilepsy New Zealand may make further comment as the proposal progresses.

Summary

Epilepsy New Zealand does not support the proposal to reduce from three funded brands to just one funded brand from 1st May 2019.

Our concern is that:

1. The risk to safety of people living with epilepsy in changing brands
2. The support of people living with epilepsy is insufficient during this proposed transition.
3. A lack of confidence and trust exists with Pharmac brand change based on past performance e.g. Efexor –XR to Enalafox-XR.
4. The cost savings expected at DHB level benefiting other than epilepsy health outcomes.

Epilepsy New Zealand believes the proposal is not in the interests of people who are currently free from seizures. Epilepsy New Zealand urges Pharmac to take further consideration of safety risks, support of those people involved and reinvestment into treatment and care of people living with epilepsy.

Epilepsy New Zealand

Epilepsy New Zealand is a non-profit voluntary membership incorporated society and registered New Zealand charity. We are the New Zealand Chapter of International Bureau of Epilepsy (IBE). We

represent a diverse membership of people living with epilepsy, their families, workplaces and community organisations.

We promote the interests of people living with epilepsy in order to positively influence the quality of life that they lead.

We accomplish our aims through practical, face to face delivery of educational services by our 15 professional educators located in our 12 offices throughout the country.

Living with Epilepsy

We estimate that there are 48,000 people in New Zealand living with epilepsy and that around six people a day will be diagnosed with epilepsy. We know at least 40 people a year will die from SUDEP (Sudden Unexplained Death from Epilepsy).

We know that 70% of people diagnosed with epilepsy will have their seizures controlled by medication.

We know that living with epilepsy creates risk of social isolation, anxiety, depression, injury, suicide and death.

Experiencing a single seizure can be devastating resulting in loss of drivers' licences, often difficulties with employment and, as a result of not being eligible for disability allowance leaving them vulnerable and able to easily enter the poverty trap.

In many cases, people living with epilepsy have social interaction problems due to isolation that they experience and lack of education. People with epilepsy are often vulnerable whether their seizures are controlled or not.

Safety Risk

Epilepsy New Zealand is aware that switching brands of antiepileptic medications carries risk as:

1. Recurrence of seizures in controlled epilepsy.
2. Seizure exacerbations.
3. Tolerability problems/side effects.

The medical advisory board noted that general batch variability exists. It also considered "in general, controlled trial did not suggest ... effect on seizures frequency; however, some of the small non-experimental cohort studies reported high switch back rates ..." These two comments from the advisory board alone means that Pharmac expects people to experience seizures because of this proposal. The GSK submission quantifies this at around 2,500 people.

Epilepsy New Zealand questions the advisory committee citing Lessing et al (2014) investigation study reporting no health outcomes measures associated with switching. Epilepsy New Zealand is a member of the Technical Advisory Improvement Services Group. This Group has the full support of the MOH data collection and yet struggles to find data in which it can be confident in relation to epilepsy outcomes .This in itself raised doubts over such measurement.

The effect of having a seizure on a person is devastating. This proposal places people who have total seizure control at risk of:

1. Loss of driving Licence.

2. Employment at risk either through lost time or loss of employment.
3. Possible WINZ assistance - People with Epilepsy are not entitled to Disability Support.
4. Mental Health Issues – level of confidence, anxiety, unpredictable psychological issues.
5. Burden on health system, individual health burden costs – Doctor visits, hospital admission, injury.
6. Level of independence.
7. Education and learning.
8. Effects on family, relationships etc.
9. Death through SUDEP, or accident such as drowning.

GSK claim that 10,000 people are affected by this proposal and that there is a 25% switch back rate. That means, as a minimum, 2,500 people are being put at risk.

Epilepsy New Zealand find that these risks to the individual are unacceptable.

Support of People with Epilepsy during Proposed Change

Pharmac are forcing people living with epilepsy to transition drugs and therefore incurring Doctor consultation costs.

Expectation is that 25% of people during this exercise will experience a seizure placing them in harm's way and at risk including death. Pharmac provides no assistance in relation to costs incurred.

Whilst the medical advisory suggest pharmacies and GPs are important in providing support and reassurance around brand change they consider the most important factor in maintaining epilepsy control is medication adherence – Pharmac provide financial assistance to HCP's yet none for the 'patient'.

Named patient Pharmaceutical Assessment guidelines have not been offered by Pharmac or guidance provided. No pathway is provided other than user pays for those required to switchback.

Epilepsy New Zealand urges Pharmac to look beyond the numbers and to take a humanitarian and holistic viewpoint to support the people it will harm from its decisions.

Pharmac Lack of Trust

Pharmac do not have a successful background in drug change.

Those that have experienced change before with Efexor –XR to Enalafox –XR have had confidence dashed by Pharmac. These people went through "a nightmare" and have been left feeling abandoned by Pharmac through misinformation, awareness, errors in dispensing and lack of engagement.

DHB Savings

It would appear from the proposal that Pharmac consider this change will provide major cost saving at DHB level. It recommends that the savings be reinvested in new pharmaceutical funding to provide improved health outcomes for New Zealanders.

Considering the risk that Pharmac is placing upon people with epilepsy, Epilepsy New Zealand considers that theses savings be reinvested into improved epilepsy health outcomes for New Zealanders.

We do not have any objections to our submission being published. We would welcome the opportunity to discuss this submission.

Yours sincerely,

Graeme Ambler
CEO/Secretary
EPILEPSY ASSOCIATION OF NEW ZEALAND INC.

M [redacted]
Email: [redacted]

To: [redacted]
From: [redacted]
Sent: Wed 26/09/2018 3:09:32 a.m
Importance: Normal
Subject: Submission for Lamotrigine proposal
MAIL_RECEIVED: Wed 26/09/2018 3:10:24 a.m
Graph 1.docx
Graph 2.docx
Appendix 2.pdf
Appendix 3.pdf
Appendix 4.pdf
[redacted] Lamotrigine submission.docx

Dear Procurement Team,

Please find attached my submission regarding the proposal for Sole Supply of Lamotrigine "[redacted] Lamotrigine submission" and attachment of relevant information.

Can you please email me back with an acknowledgment of receipt of my submission.

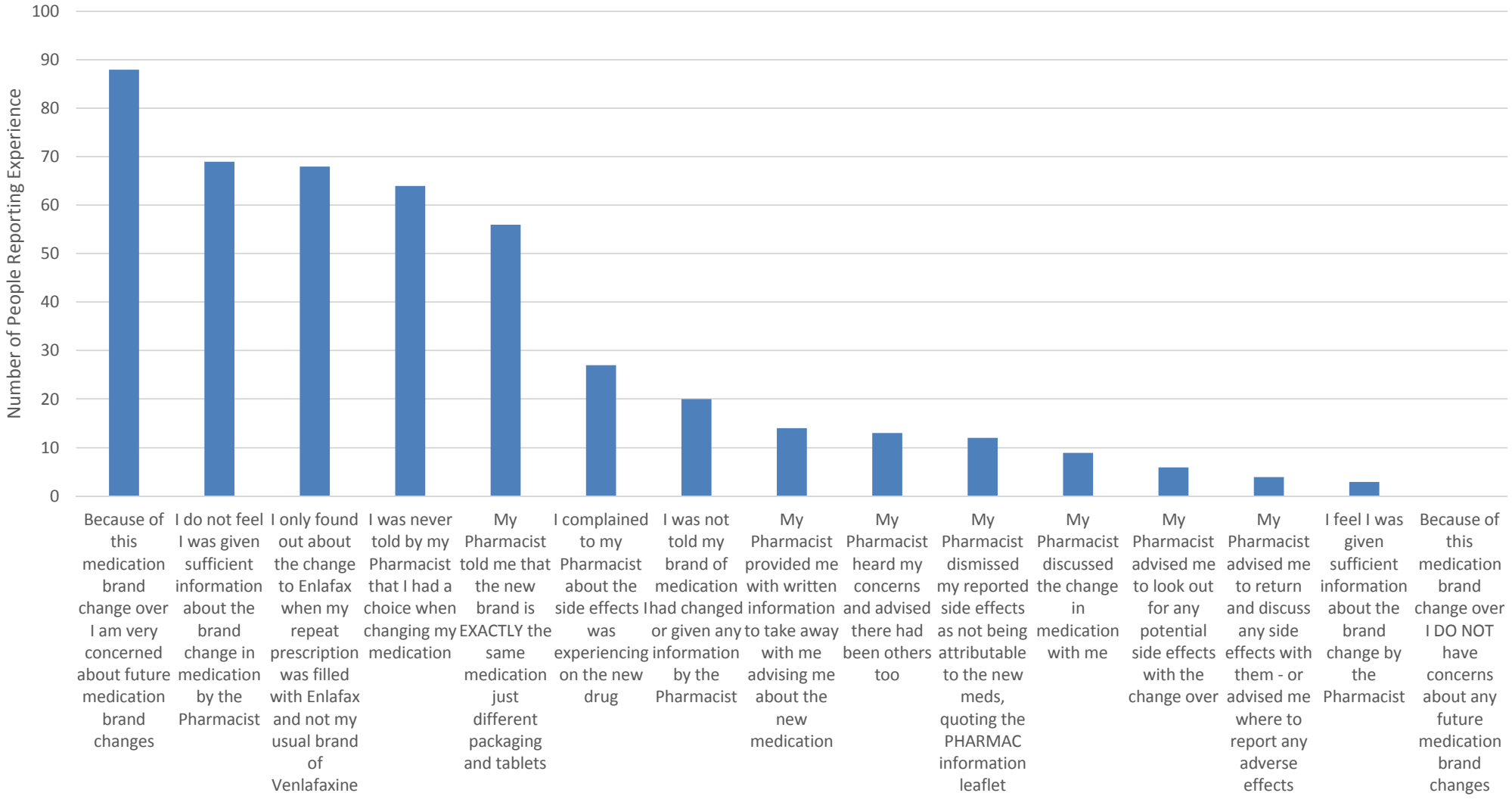
Your's Sincerely,
[redacted]

Poll of Patients Experience with Pharmicies When Changed to Enlafax

Data Collected from Poll on the Enlafax - Problems with Brand Change NZ Facebook Page

Total number of people who answered poll = **113**

Information gathered September 2018

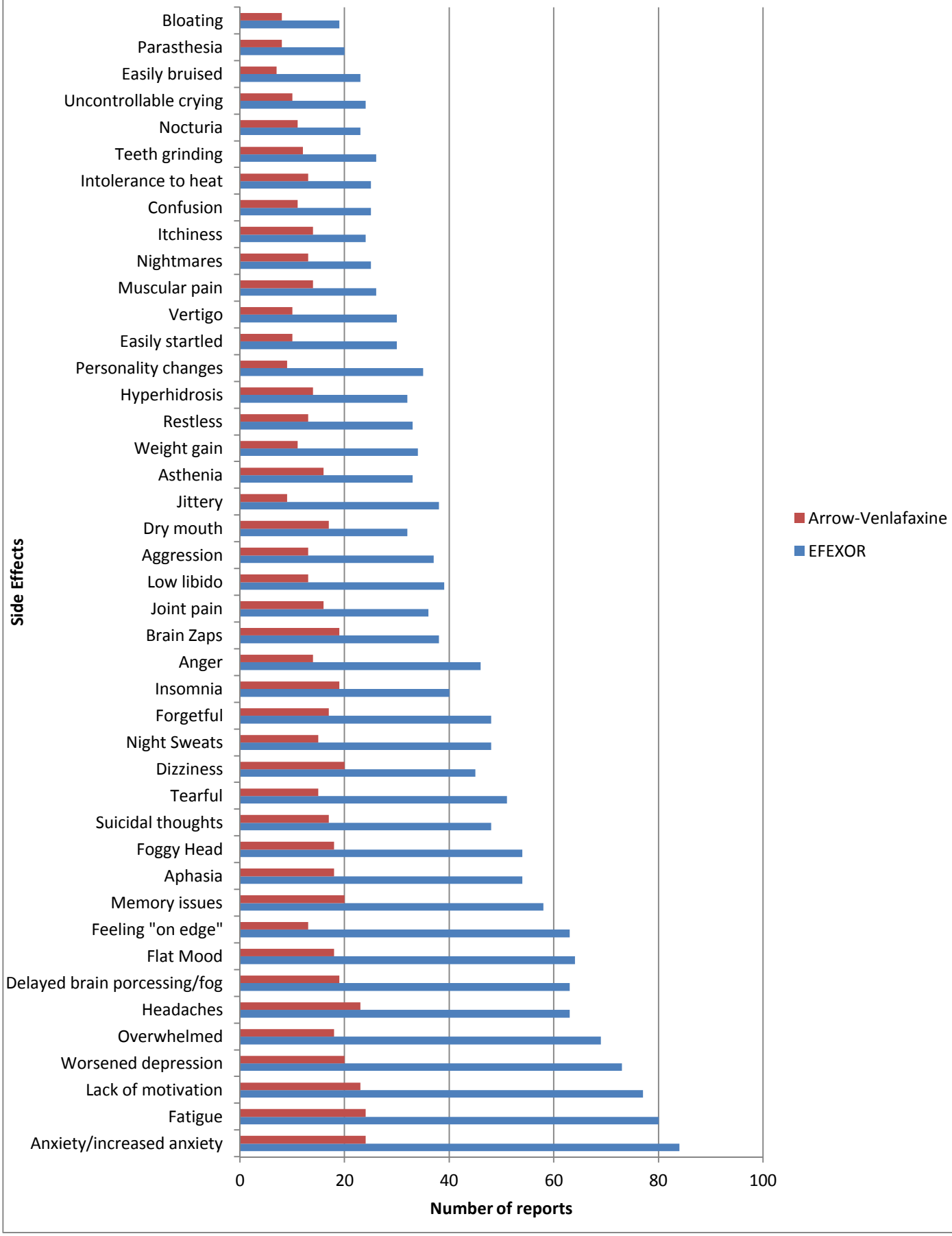


Reported Symptoms From Brand Change to Enlafax

Poll placed on Enlafax - Problems With Brand Change NZ Facebook Page

Total Number Who Completed Poll = 142

Date of Poll September 2018

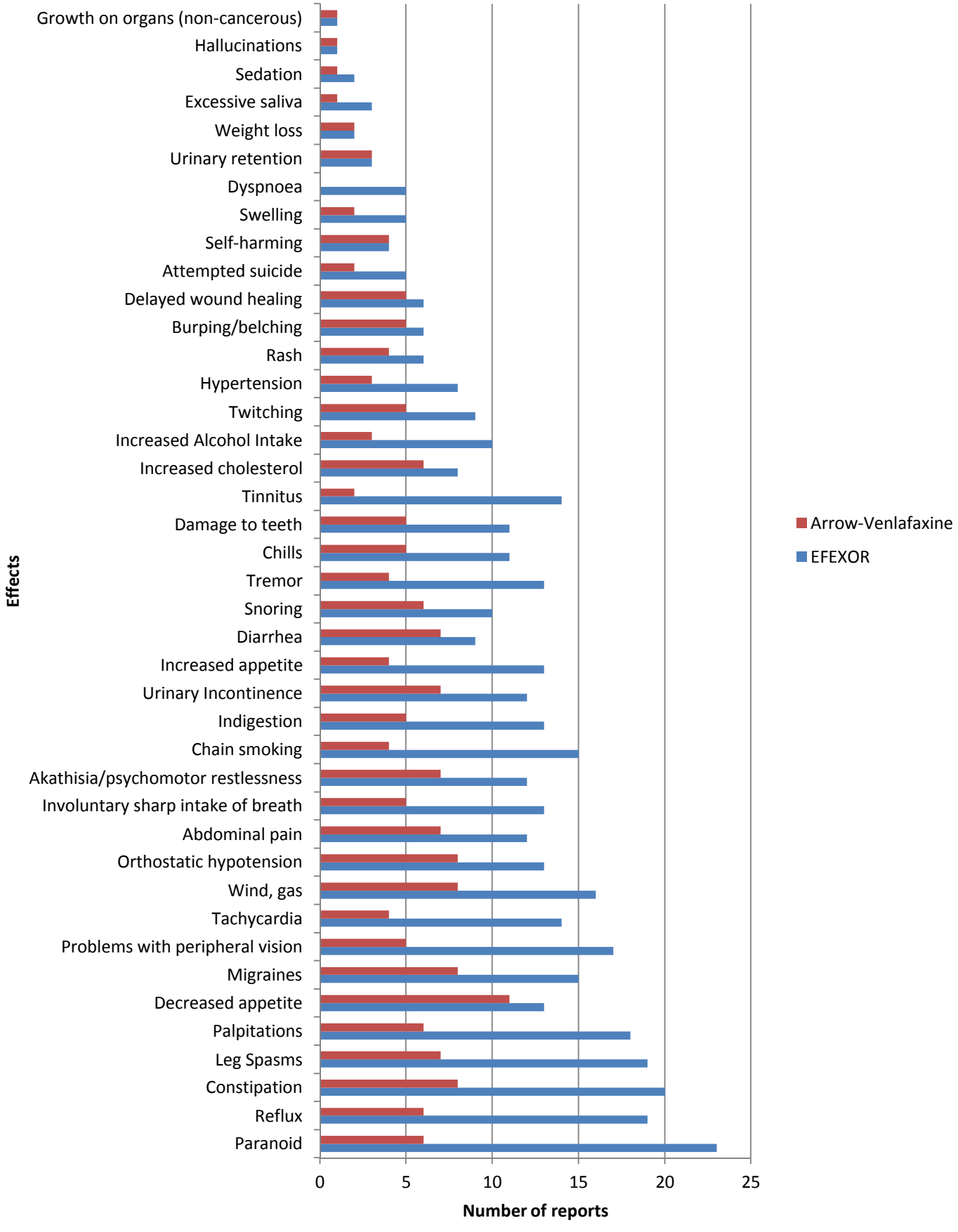


Reported Symptoms From Brand Change to Enlafax

Poll placed on Enlafax - Problems With Brand Change NZ Facebook Page

Total Number Who Completed Poll = 142

Date of Poll September 2018



PHARMAC
Pharmaceutical Management Agency

Level 9, 40 Mercer Street, Wellington 6011
PO Box 10-254, Wellington 6143, New Zealand
Phone 64-4-460-4990
Fax 64-4-460-4995
Information line **0800 66 00 50**
enquiry@pharmac.govt.nz
www.pharmac.govt.nz

3 July 2018

Via email: [redacted]

Dear [redacted]

REQUEST FOR INFORMATION

Thank you for your request dated 6 June under the Official Information Act 1982 (OIA) for information relating to the venlafaxine brand change. You asked for:

What figures and information did you use to come to the estimated savings of $5.4m (referred to notification).

The figure of $5.4 million is the estimated annual savings to the Combined Pharmaceutical Budget from the decision to fund Enlafax XR via sole supply. It is based on the forecast difference between what venlafaxine would have cost at the old prices/subsidies and the new prices/subsidies.

This cost is exclusive of GST. It does not include distribution fees (pharmacy costs).

What information was provided to GPs?

How far in advance were GPs/Psychiatrists informed of the change in these brands of medication? How did you advise health professionals of the change in medication.

I have provided a table below which sets out the specific information that was provided to GPs and other health professional groups. I have included when this information was provided, and how it was provided. For each item referred to, I have attached an online link to the published information or have provided a copy of the information in the attachment.

To assist in the timing of events, I have provided the following dates:

- 1 April 2017 – Enlafax XR became funded
- 1 June 2017 – a part payment may be charged for Efexor XR or Arrow-Venlafaxine XR
- From 1 September 2017 – only Enlafax XR is funded.

Further details can be found on our website.

Date	Information	Sent to health professionals[1]	Detail
10 August 2016	Invitation to provide feedback on proposal (consultation) by email	GPNZ, NZMA, RNZCGP, Rural GPs Network	https://www.pharmac.govt.nz/news/consultation-2016-08-09-venlafaxine
13-14 October 2016	Wānanga – included venlafaxine brand change, and follow-up email exchange	Te Āo Māramatanga Māori Mental Health Nurse wānanga	See attachment (p1-2)
17 February 2017	Presentation included venlafaxine brand change	GP leaders forum meeting	
3 March 2017	Brand change information	Published on PHARMAC website	https://www.pharmac.govt.nz/medicines/my-medicine-has-changed/venlafaxine/
3 March 2017	Upcoming changes to the brand of venlafaxine	NZMA	See attachment (p3-4)
7 March 2017	Upcoming changes to the brand of venlafaxine	GPNZ, RNZCGP, Primary Health, Rural GPs Network	See attachment (p3-4)
9 March 2017	Included in weekly stock update email	Hospital Pharmacists	See attachment
9 March 2017	Venlafaxine Brand change	RANZCP	See attachment (p6)
10 March 2017	Information on venlafaxine brand changes	NZAC	See attachment (p7-8)
21 March 2018	Venlafaxine brand change	Te Pou,	See attachment (p1-2)
21 March 2018	Venlafaxine brand change	Pharmacy Guild	See attachment (p9)
24 March 2018	Upcoming changes to the brand of venlafaxine	Mental Health Pharmacist Interest Group of the New Zealand Hospital Pharmacists' Association	See attachment (p10)
April 2017	Pharmaceutical Schedule – news story	All community pharmacists and other subscribers. Also published online	https://www.pharmac.govt.nz/2017/03/16/SU.pdf
April 2017	Venlafaxine brand change insert	Pharmaceutical Schedule subscribers	See attachment (p11-12)
24 May 2017	PHARMAC Update – included venlafaxine brand change reminder and information on generic learning module	Rural GP Network, GPNZ, NZMA, RNZCGP	https://www.pharmac.govt.nz/assets/brand-change-venlafaxine.pdf
August 2017	Venlafaxine brand change insert	Pharmaceutical Schedule	See attachment (p13-14)
10 August 2017	Presentation – included update on venlafaxine brand change	GP leaders forum meeting	

Consultation and notification documents are routinely sent to a range of interested parties, that includes health professional groups and some individual health professionals. The

[1] GPNZ: General Practice New Zealand; NZMA: New Zealand Medical Association; RNZCGP: Royal New Zealand College of General Practitioners; Te Pou: Mental health, addiction and disability workforce development; NZAC: New Zealand Association of Counsellors; RANZCP: Royal Australian and New Zealand College of Psychiatrists

venlafaxine consultation and notification were also sent to a large list of groups and individuals with an interest in the Nervous system therapeutic group. We specifically informed health professional groups (see above table) of the consultation document and invited their feedback. We also specifically notified these groups of the changes, once the change decision was made.

In addition to specific information provided to support the venlafaxine brand change, PHARMAC also took the opportunity to provide education and support for the brand change. In addition to the usual brand change information on our website, providing a page under our My Medicine Has Changed heading, we launched an online learning module aimed at health professionals to help them with communicating brand changes to their patients.

The learning module was endorsed by the RNZCGP, the Pharmaceutical Society of New Zealand and the Nursing College of New Zealand. The learning module can be accessed via Ministry of Health's LearnOnline. So far, 580 health professionals (doctors, nurses, pharmacists) have accessed the module.

PHARMAC produces its Pharmaceutical Schedule with monthly updates which outline upcoming changes. Subscribers receive a hard copy and/or electronic copy. This information is also provided in an appropriate electronic format to providers of software for pharmacy and medical practices. These providers incorporate PHARMAC funding information into their software.

How many NPPA have PHARMAC received for funding of either Efexor XR and Arrow-Venlafaxine XR since Enlafax XR became the only funded medication available? How many of these have been approved and how many have been declined?

PHARMAC has received 28 NPPA applications (25 for Efexor XR, 2 for Arrow-Venlafaxine XR and one for both brands) since May 2017. The subsidy for Efexor XR and Arrow-Venlafaxine was reduced from 1 July 2017 and funding ceased from 1 September 2018. No applications have been approved for funding.

Of the 28 applications submitted, one application (for Arrow-Venlafaxine XR) was withdrawn as the applicant did not respond to a request for additional information. For the remaining 27 applications, the NPPA core principles were not met, meaning that the application could not be progressed via the NPPA process. For these applications, the patients' clinical circumstances were not considered exceptional and there were funded alternative treatments available.

You can find out more about the NPPA policy, including details on the core principles on our website, here. Please also note that applications can be reconsidered at any time, should the applicant provide additional information.

What research studies were looked at before deciding to change to Enlafax XR?

Medsafe is the New Zealand body that assesses bioequivalence as discussed in the question below. As with any brand change decision, no specific research studies were looked at by PHARMAC before deciding to change to Enlafax XR. PHARMAC sought expert clinical advice from the Mental Health Subcommittee of PTAC prior to approving a brand change for venlafaxine.

What are the results of the bioavailability studies between Efexor XR or Arrow-Venlafaxine XR and Enlafax XR?

Medsafe assessed relevant bioavailability studies during its pre-registration assessment for the Arrow-Venlafaxine XR and Enlafax XR brands. The results show that Enlafax XR meets international standards for bioequivalence with Efexor XR.

What percentage of people who are switched to a generic brand of medication and were badly affected by adverse effects would be considered acceptable for PHARMAC? Is there a number that have to be badly affected for PHARMAC to look at funding an original medication again?

PHARMAC does not collect data on the numbers or severity of adverse effects – this role is performed by the Centre for Adverse Reactions Monitoring (CARM). We advise people to report adverse effects, including those relating to brand change, to CARM. This organisation records and investigates adverse effects to medicines and reports its findings to Medsafe, the part of the Ministry of Health responsible for medicine safety and efficacy. Should Medsafe choose to withdraw registration for a brand of medicine, it would no longer be available to fund. We would consider funding an alternative, but not necessarily the original brand.

Please note that PHARMAC approaches its assessment of requests for information under the OIA on the basis that, once released, the information becomes publicly available - in other words once we release the information to you it becomes available to any other party in that exact form (whether by you distributing it to others or by virtue of us receiving the same request from a different third party).

We have redacted a small amount of information from the attached documents as we consider this is necessary to protect the privacy of natural persons (section 9(2)(a)). We have also redacted some information on p2 and p5 of the document as it is outside the scope of your request.

As required under the OIA, we also considered whether, in the circumstances, the withholding of this information was outweighed by other considerations which render it desirable, in the public interest, to make this information available. In this case we did not consider that the public interest outweighed the reasons for withholding the information. Please note you have the right, by way of complaint under section 28(3) of the OIA to an Ombudsman, to seek an investigation and review of our decision.

We trust that the provision of these documents answers your queries, if you have any further questions please feel free to contact us again.

Yours sincerely

[redacted]

Acting Director, Engagement and Implementation

From: anthony asteriadis <[redacted]
Sent: Thursday, 11 August 2016 9:57 AM
To: Procurement
Subject: Re Proposal for Venlafaxine

Categories: Matt

Hello
Many thanks
My feedback is confidential
I[redacted]

I note also in spite of the fact that there are many new antidepressants overseas with novel actions ie Agomelatine, we have not had access to them

Sincerely
Dr a Asteriadis, psychiatrist

Sent from my iPad

From: Guna Kanniah <[redacted]
Sent: Thursday, 25 August 2016 1:33 PM
To: Procurement
Subject: RE: PHARMAC - Consultation proposal for venlafaxine

Categories: Matt

Dear Matthew,
Kindly refer to the collective input from MHSIG

While we support the saving from this proposal, we would like to highlight the following issues:

1. This is a different product from what we've had before. From the product specs(based on the Australian listing) the capsule actually contains a couple of SR tablets! (e.g.: 75 mg capsule –containing two white, round, biconvex 37.5 mg film coated tablets, 150 mg capsule - containing three white, round, biconvex 50 mg film coated tablets.) a product specification and appearance is appreciated
2. We need to know the formulation appearance. We had with the Arrow tablets was that the 37.5mg and 75mg tabs were very similar, and the 150mg and 225mg were almost identical too. Kindly ensure this new brand has some distinctions between strengths ? Esp for blister packs – are the strengths easy to differentiate?

3. Do we have data on crushing those tablets (we can crush the arrow brand, at least in the short term)? Because acute admissions on NG tubes are going to have some significant withdrawal issues if we are unable to.

4. There are currently people using Effexor caps to slowly down titrate (i.e.: having a few pellets less at each dose reduction) – mainly those whose withdrawal symptoms was awful when they went at a "usual" pace and where they can actually manage fiddling about with the pellets every day. But at least we have plenty of notice to be able to let prescribers know about the change.

5. We view with caution the proposal to have stat prescribing. Given Venlafaxine risk in overdose.
   From the Medsafe datasheet - The most commonly reported events in overdose include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Other events reported include electrocardiogram changes (e.g. prolongation of QTc interval, bundle branch block, QRS prolongation), ventricular fibrillation, ventricular tachycardia (including torsades de pointes), bradycardia, hypotension, vertigo, and death. Serotonin toxicity has been reported in association with venlafaxine overdose.

   So if Pharmac proposes to do 3 months at once (which makes sense given the pack is 84) they need to make it a safety medicine so prescribers have discretion to adjust supply where they know risk is higher.

6. One downside is the lack of the 225mg – some DHB pharmacies have changed their hospital supply to the Arrow brand as there was the 225mg strength – the loss of this will be unfortunate

Kind regards

Guna Kanniah
Convenor, Mental Health Specal Interest Group, NZHPA.
Senior Clinical Pharmacist,Mental Health and Addictions Services
Pharmacy Service,
Waikato Hospital,Hamilton
Tel[redacted]
email:[redacted]

From: Kim Dennis [mailto:[redacted]]
Sent: Wednesday, 10 August 2016 11:42
Subject: PHARMAC - Consultation proposal for venlafaxine

Good morning,

Please find attached the consultation on the proposal for venlafaxine.

PHARMAC welcomes feedback on this proposal. To provide feedback, please submit it in writing by Thursday, 25 August 2016 to:

Matthew Wolfenden
Procurement Manager
PHARMAC
E-mail: procurement@pharmac.govt.nz
Fax: 04 460 4995
Post: PO Box 10 254, Wellington 6143

All feedback received before the closing date will be considered by PHARMAC's Board (or its delegate) prior to making a decision on this proposal.

Kind regards,

Kim

Kim Dennis | Team Assistant, Operations

PHARMAC | PO Box 10 254 | Level 9, 40 Mercer Street, Wellington
DDI [redacted] P: +64 4 460 4990 | F: +64 4 460 4995 | www.pharmac.govt.nz

Actavis

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Mt Eden Business Park
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New Zealand

PO Box 128244
Remuera
Auckland
New Zealand

12th August 2017

Matthew Wolfenden
Procurement Manager
PHARMAC
P.O. Box 10-254
Wellington

By email: procurement@pharmac.govt.nz

Dear Matthew

Re: Proposal to award sole supply of venlafaxine to Enlafax XR

We refer to the consultation letter published by PHARMAC on the 10th August.

We note that -

- [redacted]
- [redacted]
- Arrow-Venlafaxine XR is already in the market and could provide savings from a considerably earlier date than Enlafax XR and well before the proposed sole supply date.
- Arrow-Venlafaxine XR has been in the market since 2011, during this time it has not been out of stock and it has not been subject to a product quality issue.
- [redacted]
- By the time of implementation of sole supply as outlined in the proposal, Arrow-Venlafaxine XR will have approximately 40% market share of all patients on venlafaxine.
- The Active Pharmaceutical Ingredient(s) listed on the Medsafe website as being used in Enlafax XR are different from those used in both Efexor XR and Arrow-Venlafaxine XR.
- We are unaware of any data on comparative bioequivalence between Enlafax XR and Arrow-Venlafaxine XR.
- Enlafax XR is to be supplied in blister packs of 14 with days of the week printed on the reverse. Blister packaging of this variety can be supplied for Arrow-Venlafaxine XR at no extra cost.
- Specific packaging requirements for 'days of the week on the reverse of blister packaging' were not outlined in the request for tender issued by PHARMAC on the 15th June 2016.
- Blister packaging with days of the week on the reverse has not been considered as important from a funding perspective for any other antidepressant or mental health product in the NZ market.
- [redacted]

We refer to the consultation published on the PHARMAC website on the 10th August -

We note that -

- PHARMAC have published a provisional proposal on their website which differs in material aspects from the provisional proposal as forwarded in the letter outlining the aforementioned provisional agreement.

With reference to process undertaken by PHARMAC staff in relation to this request for Tender.

We note that –

- [redacted]
- PHARMAC have published a provisional proposal on their website which differs in material aspects from the provisional proposal as forwarded in the letter outlining the aforementioned provisional agreement.
- [redacted]

With reference to the Operating Procedures and Policies of PHARMAC, PHARMAC's stated statutory objective is to secure for eligible people in need of pharmaceuticals the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the amount of funding provided.

We note that this proposal fails to meet this statutory objective in that –

- [redacted]
- Enforced switch for all patients taking venlafaxine will be required with the attendant risk of adverse reactions.

As a government agency PHARMAC has an obligation to ensure its procurement conduct is at all times fair, ethical, transparent and probity rich, in this instance PHARMAC has failed in this obligation.

In light of the issues highlighted above we submit that PHARMAC may have breached their duties and furthermore that entering into a contract for sole supply with Mylan for Enlafax XR may be reviewable on grounds of serious impropriety and abuse of statutory power.

Should the PHARMAC board proceed to approve this provisional agreement it will give the impression of a disregard for taxpayer funds and will also raise very serious questions for those companies providing generic medicines within New Zealand.

Sincerely
Actavis New Zealand limited

John Wickens
Business Development Manager

MINISTRY OF HEALTH
MANATŪ HAUORA

23 August 2016

179 St Hill Street
Private Bag 3015
Whanganui Mail Centre
Whanganui 4540
New Zealand
T +64 6 349 1990

Matthew Wolfenden
Therapeutic Group Manager
PHARMAC
PO BOX 10 254
Wellington

Dear Matthew

Re: Proposal to award Sole Supply of venlafaxine

Thank you for providing the Ministry of Health with the opportunity to respond to this consultation.

Based on the information contained in the consultation document dated 10 August, the Ministry of Health advise that no technical or resource impacts are anticipated as a result of your proposal.

If you would like to discuss the content of this letter, please do not hesitate to contact me by email [redacted]

Yours sincerely

Mandy Benson
Operations Analyst
Operational Support
Ministry of Health

PHARMACY GUILD OF NEW ZEALAND

24 August 2016

Matthew Wolfenden
Procurement Manager
PHARMAC
PO Box 10 254
Wellington 6143

Sent via e-mail to: procurement@pharmac.govt.nz

Dear Matthew

RE: Proposal to award Sole Supply of venlafaxine

Thank you for the opportunity to provide feedback on the above consultation.

The Pharmacy Guild of New Zealand (Inc.) (the Guild) is a national membership organisation representing the majority of community pharmacy owners. We provide leadership on all issues affecting the sector and advocate for the business and professional interests of community pharmacy.

Our feedback on this consultation focuses on Guild members' concerns around general economic, funding and supply issues. Guild submissions should not be taken as any endorsement of, or any attempt to comment on, issues of safety, efficacy or individual patient utility.

The Guild opposes the proposal to award Sole Supply of venlafaxine to Mylan for its Enlafax XR brand of modified-release capsules 37.5 mg, 75mg and 150 mg from 1 September until 30 June 2020. We acknowledge this proposal would result in significant pharmaceutical savings; we however have concerns of implications this proposal could have at the patient level.

Firstly this proposal would see no 225 mg strength of venlafaxine being listed from 1 September 2017. We previously supported the proposal to fully fund and list Arrow-Venlafaxine XR 225 mg, because a one tablet regimen is simpler and more convenient for patients. For patients currently taking the 225 mg strength of venlafaxine this proposal would result in a more complicated medication regime, which is likely to impact on patient compliance and therefore health outcomes.

Secondly, venlafaxine is indicated for the treatment of major depression, generalised anxiety disorder, social anxiety disorder and panic disorder. People with these medical conditions form a vulnerable segment of the population, and are generally averse to change. From past experiences switching brands of medicines for these patients has been challenging to say the least. For many patients a brand change is not considered an equal alternative, and can be associated with negative experiences[1]. Research shows that the flow on effects from these experiences can increase other health care costs such as hospitalisations and ED admissions. "The effects of therapeutic substitution should be carefully examined, because use of generic alternatives may not be a cost-saving strategy when total health-care costs are considered"[2]. It is of even more concern that

[1] *Patients' attitudes towards and experiences of generic drug substitution in Norway.* **Kjoenniksen, I, Lindbaek, M and Granas, AG.** 2006, Pharmacy World and Science, Vol. 28(5), pp. 284-289.
[2] *Economic Impact of Therapeutic Substitution of a Brand Selective Serotonin Reuptake Inhibitor with an Alternative Generic Selective Serotonin Reuptake Inhibitor in Patients with Major Depressive Disorder.* **EQ, Wu, et al., et al.** s.l. : 45(4), 2011, The Annals Of Pharmacotherapy, pp. 441-451.

Pharmacy House, Level 3, 124 Dixon Street, Te Aro, Wellington 6011 | PO Box 27 139, Marion Square, Wellington 6141
P. 04 802 8200 F. 04 384 8085 E. enquiries@pgnz.org.nz www.pgnz.org.nz

patients requiring the highest doses, and therefore the more serious symptoms, will have to change the number and strength of tablets as well as the brand.

If this proposal goes ahead patients will need additional information and support from their prescriber and pharmacist. To assist in providing this support it will be important that prescribers and pharmacists are provided with written information well in advance to prepare these patients for the future brand change. We also recommend you make this information available online. Venlafaxine is a long-term medication, and switching patients from one brand of medicine to another requires additional work for pharmacists and significantly more so when the medicine is for a mental health condition. For these reasons if this proposal goes ahead it is essential that there is a Brand Switch Fee (BSF) applied to all strengths of Enlafax XR from 1 September 2017.

Thank you for your consideration of our response.

If you have any questions about our feedback, please contact our Professional Services and Support Pharmacist - Sarah Bannerman, at [redacted] or [redacted].

Yours sincerely,

Linda Caddick
Professional Services and Support Manager

Actavis

T +64 9 630 4488
F +64 9 630 4490
enquiries@actavis.co.nz
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33a Normanby Road
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New Zealand

PO Box 128244
Remuera
Auckland
New Zealand

30th August 2017

Matthew Wolfenden
Procurement Manager
PHARMAC
P.O. Box 10-254
Wellington

By email: procurement@pharmac.govt.nz

Dear Matthew

Re: Proposal to award sole supply of venlafaxine to Enlafax XR

Additional to our previous response,

We note that –

- PHARMAC have clarified that Enlafax XR is to be supplied in blister packs.
- PHARMAC is proposing that the product will be subject to 3 months stat. dispensing, this will necessitate splitting of blisters with the potential for errors, wastage and spoilage.
- PHARMAC is proposing that the product will be subject to 3 months stat. dispensing, as the product is to be supplied in pk/84 this will necessitate not inconsiderable time and expense in pharmacy.
- As the product is provided in a multiple of blister packs of 14, which appears to be PHARMAC's preference, we once again see no commercial or medical reason that PHARMAC has proposed proceeding with a provisional agreement for a product with higher acquisition costs than the proposal from Actavis, wherein any multiple of blister pk/14 would have been possible.

Sincerely
Actavis New Zealand limited

John Wickens
Business Development Manager

SigJaws Charitable Trust

Christchurch Community House
301 Tuam Street, Christchurch 8011
Phone: 03 940 9470 | Mobile: 021 0243 6164 | email: s[redacted]
website: www.sigjaws.co.nz

Charities Commission Number: CC43821

Mr. Matthew Wolfenden
Procurement Manager
Pharmac NZ
Wellington

Re: Submission; Subject **"A Proposal to Award Sole Supply of Venlafaxine"**

Kia Ora Mathew and greetings.

Also many thanks for a recent telephone conversation in discussing several important aspects of the above listed issue.

Firstly will very briefly describe some quite interesting personal details about myself, which may explain the reasoning for presenting or the official lodging of this submission.

1/ am a very well-known consumer (locally, nationally and including internationally) as currently am an appointed person in solely representing Australasia on a special and extremely important International committee, entitled "Global Forum for Community Mental Health". (This committee is operated by The World Health Organisation)

2/ also am Projects Manager of a special, very busy and local community based Organisation, whom in turn provides a large amount in vital (all totally unique) supports, which regularly assists the many vulnerable folk (throughout all sections of society) whom quite often experience certain major and serious lifestyle difficulties.

3/ as a diverse (also highly unique) range in genuine and worthwhile supports is made readily available to all sections of the community in various highly specialist provided services (via SigJaws Trust) for assisting the many unfortunate people throughout the entire community.

4/ in response to this current consultation process we have made an immense amount of relevant inquiries regarding this Proposal. This includes to various organizations e.g. Medsafe NZ, Mylan NZ, (Auckland) and Alphapharm (Australia) a number of NZ Primary Health providers (General Practitioners) a well-known Christchurch Pharmacist, Te Pou, many NZ consumers and of course yourself.

5/ following a very careful and quite intense review of all this very interesting knowledge it has become quite clear

I. Little or no knowledge has been obtained from any consumer that has been prescribed (or is currently using) Enlafax XR

II. Mainly NZ Primary Health providers have submitted the appropriate and official applications to the NZ Ministry of Health for enabling the prescribing of Venlafaxine. (consequently an Arrow Manufactured version has quite often been utilized)

III. Most Primary Health Providers have emphasized that if consumers are keeping well with any type or form of Psychiatric Medication, then it is very important this is solely and continually maintained.

IV. A similar type response was received from a very well-known and local (Christchurch) Pharmacist. (various aspects of this information is enclosed)

V. A similar type response was also received from many NZ Consumers

VI. A very concerning response was received from a consumer when another generic type Anti-Depressant medication (Fluoxetine) was introduced several years ago. This person outlined [redacted] prompt feelings of extreme un-wellness when that former medication was prescribed. As a result of this totally unfortunate (also extremely, personally distressing incident and major adverse) reaction, the original medication (Prozac) was re-introduced.

VII. Medsafe NZ has not yet fully approved the public prescribing of this medication.

VIII. The current World Health Organization's guidelines on generic type (including psychiatric) medications clearly state the involved responsibilities for relevant organizations desiring to utilize these forms of medications for any health treatment.

Finally (also and including because of the above listed important issues I firmly believe it is very unwise (also possibly un-safe) for this proposal to be accepted by the Board of Pharmac NZ.

Please don't hesitate to contact me if you require any further or additional information, especially regarding any issues outlined/enclosed/attached within this Submission.

Kindest Regards,

Gary L Watts

G L Watts

Projects Manager

This submission was completed on behalf of the :	Clinical Practice Education Committee, Pegasus Health.
Address:*(street/box number)*	P O Box 741
(town/city)	Christchurch 8140
Email:	[redacted]
Organisation: *(if applicable)*	Pegasus Health
Position: *(if applicable)*	Contact person: Kathryn Henshaw, Clinical Facilitator, Pegasus Health

Proposal to award Sole Supply of venlafaxine
Consultation issued 10 August 2016

We write in response to the PHARMAC consultation issues 10 August 2016 regarding the proposal to award sole supply of venlafaxine. We do not support this proposal for the following reasons:

1) **Sole Supply**
We do not think a sole supply agreement for venlafaxine (Enlafax SR) is appropriate for the following reasons given the supply issues of other sole supply medications e.g. metoprolol, sumatriptan injection, sertraline[1]
   - Abrupt discontinuation of venlafaxine commonly causes discontinuation symptoms due to its relative short half-live. The discontinuation symptoms of venlafaxine are similar to, but can be more severe, than those produced by discontinuation of SSRIs[2]
   - Many patients taking venlafaxine have tried several other antidepressants. There may not be a clinically appropriate alternative for these patients, should an out of stock situation arise.
   - A considerable amount of time and effort by healthcare professionals is required to ensure patients with mental health conditions are adherent and stabilised on the new brand. Based on pharmacy claims data, 60% of those taking venlafaxine in Canterbury remain on the original Efexor XR brand three years after the second brand became available.
   - There is limited incentive for the current venlafaxine manufacturers (Pfizer or Actavis) to maintain registration of their products. Funding Section 29 medications to bridge the gap when registered sole supply medications go out of stock makes a mockery of the New Zealand pharmaceutical regulatory system.
   - Strategies used for the current supply issues associated with metoprolol 23.75mg include halving the 47.5mg tablet. Capsules cannot be halved.

2) **No 225mg presentation**
Based on pharmacy claims data, 489 individuals in Canterbury are currently dispensed the 225mg tablet presentation. These patients will require extra support from pharmacists to switch to a combination of the lower strength capsules (either 2 x 150mg caps plus 75mg cap, or 3 x 75mg caps). This change will also increase the patient's pill burden and potentially cost to the patient (i.e. 2 prescription charges rather than one).

3) **Stat dispensing**
We suggest that the new brand of venlafaxine (Enlafax SR) continue as monthly dispensing for a transition period past 1st September 2017 until all patients are swapped and "stable". There is at least one pharmacokinetic study in the literature of a generic venlafaxine meeting the regulatory requirements of bioavailability, but having a different release profile which led to a 3-fold increase in adverse events compared to the Efexor XR brand[3]. Encouraging this patient group to interact less with health professionals doesn't appear to be in the patient's best interests.

References

1. Ben Heather. Patients regularly face medicine shortages as New Zealand struggles to secure supply, 6th February 2016. Stuff Available at www.stuff.co.nz/national/health/76439113/Patients-regularly-face-medicine-shortages-as-New-Zealand-struggles-to-secure-supply (accessed 18 August 2016)
2. Montgomery SA, Huusom AK, Bothmer J. A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. Neuropsychobiology. 2004;50(1):57-64.
3. Chenu F et al. Comparison of pharmacokinetic profiles of brand-name and generic formulations of citalopram and venlafaxine: a crossover study. J Clin Psychiatry, 2009;70(7):958-66

CHEMO

31st August 2016

Matthew Wolfenden
Procurement Manager
PHARMAC
P.O. Box 10-254
Wellington

By email: procurement@pharmac.govt.nz

Re: Proposal to award sole supply of venlafaxine to Enlafax XR

Dear Sir

Chemo SA, Lugano Branch, is the supplier in New Zealand of Arrow-Venlafaxine XR manufactured by our factory Laboratorios Liconsa SA (CHEMO GROUP), with manufacturing facilities in Av. Miralcampo, Pol. Ind. Miralcampo, 19200 Azuqueca de Henares-, Guadalajara, Spain.

We have been notified by our license holder and distributor, Actavis NZ, that PHARMAC intends to exclude our product from the NZ market and provide sole funded access to a product supplied by Mylan.

[redacted]

[redacted]

Sincerely
CHEMO SA, Lugano Branch

Mr. Claudio Farinelli
Technical Director

Pfizer New Zealand Limited
Level 1, Suite 1.4, Building B
8 Nugent Street, Grafton, Auckland 1023
PO Box 3998, Shortland Street, Auckland, New Zealand 1140
Tel: 09 354 3065 Fax: 09 374 7630

Pfizer New Zealand Limited

1 September 2016

Matthew Wolfenden
Procurement Manager
PHARMAC

Via email: procurement@pharmac.govt.nz

Dear Matt,

RE: Response to Consultation on Proposal to award Sole Supply of venlafaxine (10 August 2016)

As you're no doubt aware, Pfizer recognises and understands the need to make financial savings within New Zealand's pharmaceutical budget.

However, Pfizer is concerned that in this case due consideration has not been given to the overall impact on patients, healthcare professionals and supply chain – especially given the Mylan proposal is likely to result in a relatively [redacted]

Pfizer currently supplies Efexor XR to around 60 per cent of the 45,000 patients on venlafaxine extended release (venlafaxine XR). Of these, the majority will be getting treatment for major depression, often refractory. These patients have chosen to continue on Efexor XR even though they are required to meet the special authority criteria to access it. This means they will have generally tried and failed at least two other antidepressants, and are likely to be more sensitive to medication changes[i1].

[redacted]

Pfizer's venlafaxine XR forecast from 1 April 2017- 30 June 2020 is summarised below:

- IMS tablet/capsule data for all venlafaxine XR brands sold in New Zealand by SKU from May 2013 to April 2016 was used as a baseline and current ratios for 37.5/75/150mg were kept as these have been consistent and stable for both currently listed brands.

- No increased use due to the removal of prescribing restrictions was modelled because Arrow's venlafaxine XR has been freely available since Special Authority was removed from Arrow Venlafaxine XR in August 2013.

- Use of 225mg tablet is assumed to be replaced by 1x 75mg and 1 x 150mg capsules.
- Growth in venlafaxine XR was assumed to gradually decline over the term of the contract: 3% in the year to June 2018, reducing to 1% in the year to June 2020, to match the growth of the population.

[redacted]

To effect this change will require significant investment in both time and resources and Pfizer notes and agrees with PHARMAC's concerns around:

- Negative response of patients to brand changes, especially those suffering from a mental illness
- Additional work required by healthcare professionals to reassure patients when these changes are imposed
- Additional resources needing to be developed to assist with the brand switch (unbudgeted)

Taking the above factors into consideration, Pfizer questions whether this savings from this proposal warrant the significant disruption to this group of patients and the additional costs to the healthcare system outside of PHARMAC's budget of implementing this change.

Yours sincerely,

Katherine Lester

Katherine Lester
Market Access Manager

[i] Appendix 1: Desmaris J E et al, CNS Neuroscience and Therapeutics 2011, 17

Clinical Advice – Email to Mental Health Subcommittee of PTAC & Responses

Dear Subcommittee members,

Please treat this email as CONFIDENTIAL information. If possible, please could you respond by Midday on Thursday 4th August as this piece of work is time sensitive.

As you may be aware, in June this year we issued a Request for Tenders (RFT) for venlafaxine and are currently going through the evaluation process.

We are currently considering the possibility of a brand switch in this market. Before we go out to public consultation later this week we would like your advice on potential implementation activities if a brand switch were to occur and the possibility of moving to stat dispensing of venlafaxine.

Current Situation

- PHARMAC currently lists and fully funds the following presentations of venlafaxine hydrochloride extended-release in Section B and Section H of the Pharmaceutical Schedule.
- All presentations have subsidy and delisting protection until 31 March 2017.

Chemical and presentation	Brand	Pack size	Current subsidy and price (ex-man, ex-GST)
Venlafaxine Tab 37.5 mg	Arrow-Venlafaxine XR	28	$5.06
Venlafaxine Tab 75 mg	Arrow-Venlafaxine XR	28	$6.44
Venlafaxine Tab 150 mg	Arrow-Venlafaxine XR	28	$8.86
Venlafaxine Tab 225 mg	Arrow-Venlafaxine XR	28	$14.34
Venlafaxine Cap 37.5 mg	Efexor XR	28	$5.69
Venlafaxine Cap 75 mg	Efexor XR	28	$11.40
Venlafaxine Cap 150 mg	Efexor XR	28	$13.98

- Arrow-Venlafaxine XR is open listed, whereas Efexor XR is restricted via Special Authority (SA1061) for patients with treatment-resistant depression.
- The RFT was for an open listed product ie no clinical restrictions would apply.
- The current annual expenditure is $8.4 million in the Community (FYR ending 2015) – #18 medicine by cost (Jan 2016)
- $7.22 million expenditure was for the Pfizer Efexor XR capsules and $1.16 million was on the Actavis Arrow-Venlafaxine XR tablets.
- Financial Year Ending 30 June 2015 – Number of patients approximately 41,000 (29,000 Chronic = 70%)

Advice

1. PHARMAC staff realise that switching ~40,000 patients in this patient group would require excellent communications and information for GPs, pharmacists and patients. Do you have any specific advice around additional implementation activities required for a brand switch in this market? i.e. beyond targeted information for patients (hardcopy & website), a brand switch fee paid to pharmacists to assist with a switch, written education for primary care, and communicating with stakeholder groups such as RNZCGP, RANZCP and Mental Health Foundation.

[redacted]

26 September 2018

procurement@pharmac.govt.nz

RE: Proposal to move to one funded brand of Lamotrigine (Logem).

Submission prepared by [redacted], email – [redacted]

Dear Procurement Team:

I give permission for the information provided in this submission to be used for any requests under the Official Information Act.

This submission is based on information from the Pharmac® website about the Lamotrigine proposal including advice and recommendations provided by the Mental Health Subcommittee and the Neurological Subcommittee. I will include supporting information and evidence about problems with the Psychotropic drug Venlafaxine. Myself and hundreds of other people suffered serious adverse effects from the brand change over despite plans for implementation in place – similar to what has been noted for the Lamotrigine proposal.

If the proposal to move to a sole supply arrangement is implemented, there is risk for severe harm to people who are currently stable on Lamictal or Arrow-Lamotrigine.

I have a number of concerns about this proposal. Previous strong psychotropic medicines were changed from branded names to generics. The lack of patient safety protocols resulted in many patients suffering severe harm, and in some cases lives were lost. The most recent example I will show supporting evidence from is the changeover from Arrow Venlafaxine® and Efexor XR® to Enlafax XR®.

I have the following concerns:

1. The continued lack of information and support for people taking these medications by the Pharmacists:

- Failure to advise people their brand of medication has changed.
- Failure to inform people they have the option to stay on their current brand of medication if they wish to
- People being forced to change to Logem®.
- Pharmacists receiving a brand switch fee for every person who has been changed to Logem® without providing information or support to those affected.

2. The increased potential for adverse reactions for some people who have been changed to Logem®:

- People not being informed there is a potential for adverse reactions to occur.
- Health professionals not being fully aware of the changes with Lamotrigine® thereby putting people at risk because of delays in recognition of brand change related deterioration in health status.
- Increased health care costs to the individual if they experience adverse reactions to Logem®.

3. Deterioration of individuals who are stable on current medications. In particular, individuals with epilepsy can experience reoccurrence of previously controlled seizures with changes to the generic Lamotrigine (Logem). Deterioration because of medication changes will result in increased demand for health services, and increased costs to the individual.

   There is research available about changes to generic Lamotrigine for people with epilepsy and a reoccurrence of previously controlled seizures. (see appendix)

- Increased potential for re-occurrence of currently well managed Bi-polar symptoms.
- 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.
- Potential for increased doctor's visits.
- Potential for re occurrence of seizure activity.
- Potential risk for seizure activity occurring whilst a person is driving or at work resulting in injury or fatality to themselves and/or other road users, public or colleagues.

A person's Quality of Life may be severely impacted by any of the above occuring including but not limited to:

- Loss of drivers licence.
- Loss of employment.
- Loss of accommodation.
- Relationship breakdowns.
- Financial instability.
- Deterioration in health.

Finding a medication which works and has manageable side effects can take a long time and the risks associated with trialling many different medications makes people extremely vulnerable.

- Changing a person from a medication they are stable on to a generic brand there is the potential a person may not tolerate the change and the implications for this can be huge.
- Regaining stability if serious adverse effects occur can take many months, if not longer.

Questions arising from Proposal to move to one funded brand of lamotrigine (Logem)

1. What are the anticipated savings to Pharmac if this proposal is implemented?
2. Was the tender from Mylan the most cost effective tender submitted?
3. Has the NZTA been advised of this proposal?
    a. What are their recommendations regarding this proposal?
    b. How have PHARMAC responded to these recommendations?
    c. Have PHARMAC considered the impact the loss of drivers licence will have on a person's independence and Quality of Life if seizure activity occurs because of a change to generic Lamotrigine?
4. 5000 people are currently taking Lamotrigine for epilepsy according to information about this proposal from the PHARMAC website.
    a. With medsafe's expected 1% reactions this equates to approximately 50 people driving that could experience a seizure. As a precaution should the NZTA

introduce a stand-down period for all patients switching in the interests of public safety?

b. What communications will you be giving to patients and medical professionals around these risk and how to manage them?

5. Have Worksafe been advised of this proposal?

   If a person has well controlled Epilepsy with Lamictal or Arrow-Lamotrigine and happens to operate heavy machinery there is potential for Workplace accidents to occur which may result in injury or fatalities of the person and also others around them.

6. Under the heading "What would the effect be? For patients" "Prescribers, pharmacists and patients would be supported with information and implementation activities to manage any change."

   a. How will PHARMAC consult with healthcare providers to ensure they are informed of possible symptoms to adverse events and/or patient deterioration and have the resources to accommodate this group of individuals?
   b. How will this information will be provided?
   c. How far in advance would all of these groups be advised of the change?
   d. What information will be included?
   e. What are the implementation activities?
   f. Does PHARMAC have any follow-up in place to ensure patients are being informed and educated about the brand changes?
   g. What more will PHARMAC do in this roll out to address the major shortcomings as compared to their attempts at communication with the brand change to Enlafax; during which a vulnerable group of patients suffered major relapses leading to self-harm and attempted suicides.

7. The brand switch fee for Pharmacists:
   The brand switch fee for the change to Logem would be approximately **$72,000** (12,000 people taking current brands x $6 per person changed).
   a. Are pharmacists required to provide evidence they have provided support and education to people before receiving the brand switch fee?

[redacted]

Concerns arising from Neurological Subcommittee of PTAC held 11 November 2015:

"3.12 The Subcommittee considered the MHRA categorisation to be pragmatic and were 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."

Correct categorisation of antiepileptic drugs is essential and ensures people are not placed at unnecessary risk. It is unsafe for a proposal like this to be implemented when such a significant classification cannot be agreed on by the experts in this field which Pharmac rely on for accurate information.

The difference between category one and category three is significant:

Category one – Doctors are advised to ensure their patient is maintained on a specific manufacturer's product.

Category three – It is usually unnecessary to ensure that patients are maintained on specific manufacturers product unless there are specific concerns.

It is concerning the Subcommittee have not been able to reach a consensus on which category Lamotrigine fits into considering the potential risks of seizures when changing to generic Lamotrigine, and therefore an increase in healthcare costs.

Without a consensus on this issue people may potentially be given a generic form of medication which may not be suitable for and put them at risk of harm.

"3.22 Members considered that patients could be considered through the NPPA pathway if they were unable to transition for exceptional circumstances"

It is evident accessing funding through a NPPA is very restrictive. All 28 NPPA's applied for were declined by Pharmac for Efexor and Arrow-venlafaxine as per the letter dated 3 July 2018 from Pharmac (see appendix 2).

"3.25 The subcommittee expressed the importance of HCPs providing support and reassurance around brand changes and considered that the most important factor for maintaining epilepsy control was medication adherence."

"3.26 The Subcommittee considered that GPs and pharmacists would be the HCPs most likely to be involved in supporting a brand change for lamotrigine, should this occur."

As per the evidence provided information is not getting through to all the people who have had their brands of medication changed (Graph 1). People who are already vulnerable are at further risk of harm because the plans are not followed by all HCP's.

In my experience many HCP's were not aware of the brand change of medication until after it occurred and people experienced deterioration in their health. Some Doctors are still unaware of the brand change to Enlafax which occurred over a year ago.

How can HCPs provide people with information when they are not aware of the changes that have occurred?

Submissions for the Sole Supply of Enlafax provided significant amount of information regarding the importance of providing support and excellent communication for people changed to Enlafax. Plans included having:

- A brand switch fee,
- Providing information to Doctors and Pharmacists,
- Information pamphlets to be given out by Pharmacists.
- Online information about the brand change over were available.

Despite all of these plans in place many people experienced severe life-threatening adverse effects and were not provided with the support or communication required to ensure a safe transition to Enlafax occurred. (Graph 1 & 2)

PHARMAC were aware of the need for "excellent communication" as per "Clinical Advice – Email to Mental Health Subcommittee of PTAC & Responses" (see appendix 4), this did not happen for all people who were changed to Enlafax and resulted in significant deterioration in peoples previously stable condition with new or worsening symptoms. "**1.** PHARMAC staff realise that switching ~40,000 patients in this patient group would require excellent communications and information for GPs, pharmacists and patients. Do you have any specific advice around additional implementation activities required for a brand switch in this market? i.e. beyond targeted information for patients (hardcopy & website), a brand switch fee paid to pharmacists to assist with a switch, written education for primary care, and communicating with stakeholder groups such as RNZCGP, RANZCP and Mental Health Foundation."

Given the lack of information provided for recent brand changes in medication and PHARMAC's awareness of the need for "excellent communication" (see appendix 4), how will Pharmac ensure that the implementation plans and information is actually provided to people?

What will Pharmac put in place to ensure ALL Doctors are aware of this change in brand of medication?

My concerns about this proposal originate from the change to Enlafax-XR. The graph provided titled "Experiences with Pharmacy" (Graph 1) demonstrates a lack of information and support when changing brand of medication from Pharmacists:

Of the 113 people who responded to the poll on the Facebook Page "ENLAFAX – problems with medication brand change NZ":

- 14 people were given pamphlets about the brand change (developed by PHARMAC).
- 20 people were not advised their brand of medication had changed.
- 56 people were advised the medication was exactly the same as their current brand.
- 64 people were not advised there was a choice to stay on their current brand of medication.
- Very few people were advised of the potential for adverse effects to occur.
- When adverse effects did occur many people's concerns were ignored or dismissed by Pharmacists/Doctors.
- The adverse effects experienced by a lot of people have been debilitating and severe. Considering people were advised the medication would work the same, and no mention of adverse effects, many people were at undue risk.
- I have attached a copy of a graph with results from a recent poll about side effects experienced by 142 people who were changed from Arrow-venlafaxine and Efexor to Enlafax.

Experiences from people affected by the brand change to Enlafax:

- People were told the medication would work the same.
- The potential for adverse reactions to occur were not discussed.
- High costs involved for health care needed after a rapid deterioration for me this included:
    - $400 to see a Psychiatrist privately for a review.
    - Four ambulance bills within a four week period $392.
    - Cost of Efexor-XR, $51.60 a month.
    - Substantial time off work and loss of wages.
    - Admissions to medical wards and Mental Health ward, two weeks in total.
    - Respite care.
    - Going back under the care of Community Mental Health Team with regular appointments with a key worker and Psychiatrist.

The extra health care I have required because of the impact from a brand change to generic venlafaxine has been extensive. It would have been much more cost effective to stay on Efexor-XR which I was stable on rather than what I experienced.

[redacted]

Questions arising from Mental Health Subcommittee of PTAC held 23 November 2016:

"5.1 The Subcommittee considered that it would not be clinically problematic from a mental health standpoint to switch patients from one brand to another if necessary (ie. No more or less problematic than any other mood stabilizer brand change), although it would require additional work by pharmacists to reassure patients who were switched."

"5.2 The Subcommittee considered that a lamotrigine brand change in patients taking it for mental health indications would be unlikely to require additional clinic visits".

"5.4 The Subcommittee considered that Pharmac's usual brand switch activities would be sufficient to support a lamotrigine brand change from a mental health perspective. The Subcommittee noted that because lamotirigine is in its own class, pharmacologically speaking amongst mood stabilisers, some patients may be particularly dependent on it psychologically and may need extra support."

Are the Mental Health Subcommittee aware that the usual brand switch activities are not being followed by a number of Health Professionals and people are being put at undue risk because of this?

There has been an increase in health care service usage since the brand change over including a lot of extra support required from Mental Health Services.

My experience with the Enlafax brand change and the lack of support I received:

> I deteriorated within a three week period to being very unwell mentally and having constant thoughts of self-harm and suicidal thoughts. I tried to get support from Community Mental Health Services but was advised as I was not currently under their services they could not help without a new referral from my GP.
>
> To get an appointment to see my GP at that time was around a three week wait.
>
> I attended the acute walk-in clinic and advised them I was feeling suicidal and concerned about the potential to self-harm due to my significant history. I was not given and follow-up, or support – was left to manage the change alone despite my history.
>
> After my first overdose due to the change in brand of medication I was advised Mental Health would ensure a support plan was put in place before I was discharged – this did not happen.
>
> A few days later I had a second significant overdose, I was still waiting for the support that was meant to be implemented during my first admission to the hospital.

[redacted]

Considering Mental Health Services are currently in crisis and getting timely help is already difficult, I would like to know:

1. What will you put in place to ensure people who are affected by the brand changeover will get the support they require?
2. How will the people who are affected be identified?
3. As per the information I have provided with the graphs, it is evident a lot of people were not given information regarding the brand change over for Enlafax, this put many people at risk. How can this be prevented from happening this time around?
4. I notice that you mention "some patients may be particularly dependent on it psychologically and may need extra support": What steps will be put in place to ensure these particular patients receive the extra support they require for this brand change?

Consequences and implications associated with changing to generic medication; written by [redacted]

The impending funding switch to a singular brand for Lamotrigine has begun having a detrimental effect on my mental health. The fear of this change can be paralysing, and is very real for many of us who are aware of the proposed change. Since becoming aware of this, anxiety regarding this change has been intense, and thoughts of hopelessness have returned. This change has also triggered feelings of "what is the point", with yet another change to what was working for me, and so many others.

I am one of the unfortunate people who have suffered severe adverse effects of the switch to the generic brand of Venlafaxine, Enlafax-XR. These primarily relate to a significant increase in active suicidality (7 admissions to [redacted] in the past [redacted] with an 8th looming), increased irritability, and a severe drop in my mood.

I have been prescribed Lamotrigine in the capacity of a mood stabiliser, with queries of me suffering absence seizures prior to taking this medication. Rather than as a treatment for Bi-Polar, it is used to treat symptoms of Borderline Personality Disorder, which have been well managed on Arrow-Lamotrigine. Given the adverse reaction to Enlafax-XR, a switch to another generic is terrifying, and I feel it runs the risk of this happening again. I am on many medications that interact with each other; Venlafaxine, Lamotrigine, Mirtazapine, Rizatriptan, Gabapentin, Baclofen and Levomepromazine. I am concerned an alternative make-up of Lamotrigine will alter how other medications are absorbed and interact with one another. There is also concern from both my family and myself, that a change in the medication will bring back the long periods of "blanking" or "staring in to space" that I was suffering – which reduced once taking Arrow-Lamotrigine. We are concerned that the active suicidality will increase further, and remaining on the unfunded medications (Arrow-Venlafaxine and Arrow-Lamotrigine) is not an option for us financially.

APPENDIX

APPENDIX 1 – supporting research:

Crawford, P., Feely, M., Guberman, A., & Kramer, G. (2006). Are there potential problems with generic substitution of antiepileptic drugs?: A review of issues. *Seizure 15*(3) 165 – 176. Retrieved from https://www.sciencedirect.com/science/article/pii/S1059131106000033

LeLorier, J., et al (2008). Economic impact of generic substitution of lamotrigine: projected costs in the US using findings in a Canadian setting. *Current Medical Research and Opinion. 24*(4) 1069 – 1081. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18315941

Conclusion: Use of generic lamotrigine in Canada was significantly associated with increased overall medical costs compared to brand use. Projected overall US health care costs would likely increase as well.

Wick, J.Y. (2014). Switching Antiepileptic Drugs: Benefits Versus Risks. *Pharmacy Times.* Mar 2014. Retrieved from https://www.pharmacytimes.com/publications/issue/2014/march2014/switching-antiepileptic-drugs-benefits-versus-risks

End Note

Controversy about switching AEDs continues. The American Epilepsy Society and the American Academy of Neurology recommend against switching from brand to generic AEDs without prescriber and patient permission.[13] The most prudent approach is to be sure that patients and their health care teams weigh the risks and benefits of switching, and remain suitably vigilant during the switch. Although changing AEDs can be emotionally difficult for patients, it is also an opportunity to improve seizure control and/or reduce adverse effects.

APPENDIX 2 (see attached document in email), page 3.

APPENDIX 3 (see attached document in email)

Page 6 and 7 – Pharmacy Guild of NZ.

Page 10 – Clinical Practice Education Committee, Peagusus Health.

APPENDIX 4 (see attached document in email).

From: [redacted]
Sent: Wednesday, 26 September 2018 7:39 a.m.
To: Procurement
Subject: Lamotrigine

Follow Up Flag: Follow up
Flag Status: Flagged

Just wanted to express my concern about you changing to funding one brand of lamotrigine. As I'm sure you're aware with any brand change, there is always a small percentage of people that the new brand doesn't agree with. When its something like Losec and the person is experiencing reflux upon changing brands, its not a big deal (in the scheme of things). But if an epileptic has finally managed to get their seizures controlled on a particular brand and dose of lamotrigine and you take that away from them there are HUGE repercussions. E.g. If the brand change upsets their seizure control, they could lose their license, have a serious accident etc etc. This can hugely impact their life and the lives of their family and employers. I'm completely against forcing everyone to change to Logem. It's concerning that you'd even consider it.

[redacted]

25.9.18

To PHARMAC

Dear Members of the Board,

Herewith my husband and I would like to take up on the invitation to provide you with our feedback and concerns regarding your proposal to only fund one brand of lamotrigine.

Firstly, I would like to ask, why have patients not been notified by pharmacists and/or the medical profession?

We are aware that switching brands of anti epileptic medications carries risks such as:

- Recurrence of seizures in controlled epilepsy
- Seizure exacerbations
- Tolerability problems / side effects

We are now particularly concerned for my husband who has achieved seizure control some years ago on a combination of Lamictal and Epilim - please note - after years of trying and fine tuning various anti-epileptic drugs and dosages. He will now be at risk of seizure recurrence with all its possible implications on:

- Driving
- Career
- Safety
- Mental health & emotional wellbeing (possible anxiety, depression)
- Cognitive functioning and memory
- Burden on health system (increased doctor's visits, hospital admissions, injury etc.)
- Level of independence / confidence
- Financial situation
- Effects on family, relationships etc. etc.

Simply one seizure can have so many repercussions for him and in return, on society at large. The costs of the possible negative outcomes can be very high and may far outweigh funds saved by switching to generic medication. This surely cannot be underestimated. Also, should switching back to the original brand

be required, he may not necessarily obtain the seizure control he had prior to the changes.

My husband is an [redacted] Again, it has taken him a long time to fine tune his medication regime in order for him to simply feel well, obtain seizure control, gain confidence and lead a normal life.

Newly prescribing of generics may be acceptable, but people already on branded versions should have the right to be consulted and be able to object to change without being penalised with an extra manufacturer's surcharge.

If PHARMAC would be considerate of the best health outcomes, the proposal must not go ahead. Wouldn't PHARMAC need to take a much more gradual approach and be more considerate of the potential risks? Otherwise, could exemptions be considered for those on branded versions of lamotrigine with current seizure control? The risks are too great to ignore! We hope that PHARMAC will take on a much more supportive role.
My husband and I would like to see PHARMAC continue to fund the branded versions of lamotrigine.

Thank you for your consideration.

Yours sincerely,

[redacted]

MINISTRY OF HEALTH
MANATŪ HAUORA

10 September 2018

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Whanganui Mail Centre
Whanganui 4540
New Zealand
T +64 6 349 1990

Therapeutic Group Manager
PHARMAC
PO BOX 10 254
Wellington

Re: Proposal to move to one funded brand of Lamotrigine (Logem)

Thank you for providing the Ministry of Health with the opportunity to respond to this consultation.

Based on the information contained in the consultation document dated 29 August, the Ministry of Health advise that no technical or resource impacts are anticipated as a result of your proposal.

If you would like to discuss the content of this letter, please do not hesitate to contact me by email mandy_benson@moh.govt.nz

Yours sincerely

Mandy Benson
Operations Analyst
Operational Support
Ministry of Health

The Royal Australian & New Zealand College of Psychiatrists
Tu Te Akaaka Roa
New Zealand National Office

Your Health in Mind

21 September 2018

Mr Marc Haughey
PHARMAC
PO Box 10 254
Wellington

By email: procurement@pharmac.govt.nz

Dear Mr Haughey

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

Thank you for the opportunity to comment on the proposal to change the funding of lamotrigine dispersible tablets used in the treatment of bipolar disorder. The Royal Australian and New Zealand College of Psychiatrists (RANZCP) understands that from 1 May 2019 Logem will be the only funded brand of lamotrigine (available in 25mg, 50mg and 100mg) dispersible tablets in both the community and hospital setting. The RANZCP has reviewed the proposal and supports this proposal in principle.

The RANZCP's comments on the proposal

From an operational perspective it is important to ensure patients are supported in this transition. Some individuals will believe that this medicine is different from their current medicine, therefore, may feel it is not as effective as the current product. Subsequently, we suggest careful messaging is developed to assist the person in adjusting to the new formulation. For example, if the new tablets look different from current products, then information will need to be provided to those living with a bipolar disorder to reassure them that this product has similar characteristics to one they are currently using. We note that prescribers, pharmacists and consumers will be provided with the relevant information about the change and this should assist in reducing any anxieties associated with the new proposed funding model.

The only concern the College has regarding moving to the one funded brand is 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. We strongly support a process where consumers may be assisted in seeking alternative treatment options as a consequence of this transition.

Thank you for seeking our views on the proposal regarding the funding of lamotrigine
If you have any further questions regarding this letter please contact the RANZCP's National Manager New Zealand, Rosemary Matthews who supports the New Zealand National Committee. Rosemary can be contacted on [redacted] or by email [redacted]

Ngā mihi nui

Dr Mark Lawrence FRANZCP
Chair, New Zealand National Committee
Tu Te Akaaka Roa

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NEW ZEALAND LEAGUE NZLAE AGAINST EPILEPSY

Bronwyn Locke
Implementation Lead
Engagement and Implementation
Pharmac

Sept 22nd 2018

Dear Bronwyn,

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

Thank you for consulting with the New Zealand League Against Epilepsy (NZLAE) on the issue of single brand funding of lamotrigine.

We do not have any issues with the proposal but we would like to bring the following points to your attention:

1. It is important that the changing of brands is managed well at the pharmacy level. Patients need to be well informed that the new brand is the same AED even though it looks different. They need to be informed that the change will not impact on their seizure control.
2. It is imperative that we continue to have funded 2mg and 5mg tablets. We appreciate this is the intention as per the proposal but we have some anxiety that this may become an issue when the other brands no longer have their larger tablets funded – has Pharmac secured supply with the companies that provide these 2mg and 5mg tablets given none of their other tablets will be funded?
3. If there is only one funded brand supply is a concern. It would be a disaster for people with epilepsy if there is a supply issue. We trust that Pharmac has appropriate contingency plans for any problems with supply of the single funded brand.
4. It is important that people with epilepsy are given 3 months supply of the lamotrigine (and their other AEDs). Epilepsy is a chronic disease and as such, individuals should not need to go to a pharmacy every month to get their AED. Many of them do not drive and it can be difficult for them to get to a pharmacy every month.

Yours sincerely

Associate Professor Lynette Sadleir, MB.ChB., Dip Paeds, FRACP, MD
President of the NZLAE

PHARMACY GUILD OF NEW ZEALAND

26 September 2018

PHARMAC
PO Box 10 254
Wellington 6143

Sent via email to: procurement@pharmac.govt.nz

Dear Sir/Madam

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

Thank you for the opportunity to provide feedback on the above consultation.

The Pharmacy Guild of New Zealand (Inc.) (the Guild) is a national membership organisation representing the majority of community pharmacy owners. We provide leadership on all issues affecting the sector and advocate for the business and professional interests of community pharmacy.

Our feedback on this consultation focuses on Guild members' concerns around general economic, funding and supply issues. Guild submissions should not be taken as any endorsement of, or any attempt to comment on, issues of safety, efficacy or individual patient utility.

The Guild opposes the proposal to move to one funded brand of lamotrigine (Logem), 25 mg, 50 mg and 100 mg dispersible tablets from 1 May 2019 until 30 June 2022. We acknowledge this proposal would result in pharmaceutical savings, however, the savings from changing approximately 12,000 people to only one funded brand of lamotrigine would be insignificant when counterbalanced by the implications this proposal could have at the patient level.

Lamotrigine is indicated for the treatment of epilepsy and bipolar disorder. People with these medical conditions form a vulnerable segment of the population and are generally averse to change. Past experiences switching brands of medicines for these patients has been challenging to say the least. For many patients a brand change is not considered an equal alternative and can be associated with negative experiences[i]. Research shows that the flow on effects from these experiences can increase other health care costs such as hospitalisations and ED admissions.

Our members have provided us with feedback about their concern for those patients who have experienced issues with seizure control when there was a previous brand switch from Lamictal to a generic lamotrigine which necessitated switching back to Lamictal. The New Zealand Transport Agency requires the period without seizures to be 12 months before considering the epilepsy to be controlled. A move to having just one funded brand of lamotrigine (Logem) available will adversely affect these patients.

We would be supportive of reducing the subsidy of the currently listed brands of lamotrigine 25 mg, 50 mg and 100 mg dispersible tablet (Arrow-Lamotrigine and

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Lamictal) to the proposed subsidy for Logem and applying a manufacturer's surcharge when these brands are dispensed. Although this will mean patients would be required to make a part payment for their prescription, it will provide patients with continuity of access and allow for better patient outcomes.

Thank you for your consideration of our response. If you have any questions about our feedback, please contact our Professional Services Pharmacist, Linda Joe, at [redacted] or [redacted]

Yours sincerely,

Nicole Rickman
General Manager – Membership and Professional Services

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[i] *Patients' attitudes towards and experiences of generic drug substitution in Norway.* **Kjoenniksen, I, Lindbaek, M and Granas, AG.** 2006, Pharmacy World and Science, Vol. 28(5), pp. 284-289.

Angeliqe Nel

From: Kim Hawe <[redacted]
Sent: Monday, 1 October 2018 4:28 PM
To: Janet Mackay
Subject: [SPAM]? PHARMAC consultation - epilepsy medicine - proposed brand change for lamotrigine

Good afternoon Janet

Please find below comments from our Chief Medical Advisors in response to proposed brand change for lamotrigine

This shouldn't be of concern to NZTA as it is just a 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.

Kind regards

Kim Hawe /Manager Medical Reviews

DDI [redacted]
E [redacted] W nzta.govt.nz

Palmerston North Office Private Bag 11777, Palmerston North 4442, New Zealand

Find the latest transport news, information, and advice on our website:
www.nzta.govt.nz

Angeliqe Nel

From: David Hutchinson (ADHB) [redacted]
Sent: Wednesday, 29 August 2018 4:49 PM
To: Procurement
Subject: PHARMAC Consultation: Proposal to move to one funded brand of Lamotrigine

Follow Up Flag: Follow up
Flag Status: Flagged

Categories: Tim

Attn: Marc Haughey

Marc, I support the proposed change to a single funded brand of lamotrigine. 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 clinicans. Savings can be applied elsewhere in the health system.

Regards,
David Hutchinson.
Neurologist
Auckland City Hospital.

Angeliqe Nel

From: John Mottershead <[redacted]
Sent: Wednesday, 29 August 2018 4:53 PM
To: Procurement
Subject: Lamotrigine
Attachments: Holtkamp_et_al-2018-Epilepsiabrandswitch.pdf

Follow Up Flag: Follow up
Flag Status: Flagged

Categories: Tim

I support the proposed change to single available formulation of lamotrigine.

The attached 2018 review is also supportive, both for AEDs in general and lamotrigine in particular.

John Mottershead

Angeliqe Nel

From: Marc Haughey
Sent: Friday, 31 August 2018 8:07 AM
To: Procurement
Subject: FW: PHARMAC Consultation: Proposal to move to one funded brand of Lamotrigine

Please see below.

Marc Haughey | Team Assistant, Operations

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[SEEMail]

From: Paul Timmings <[redacted]
Sent: Thursday, 30 August 2018 1:29 PM
To: Marc Haughey <[redacted]
Subject: RE: PHARMAC Consultation: Proposal to move to one funded brand of Lamotrigine

Dear Marc.
I support this change but am concerned that the 2mg and 5mg size supply chain may become vulnerable if the makers of those items were not supplying the full range.
It would be important to obtain a commitment from them to continue to supply those sizes. Maybe they could be given sole supply of those sizes too.
Paul Timmings

From: Marc Haughey [[redacted]
Sent: Wednesday, 29 August 2018 4:41 p.m.
Subject: PHARMAC Consultation: Proposal to move to one funded brand of Lamotrigine

Good afternoon,

Please find attached a consultation on the proposal to move to one funded brand of lamotrigine.

Consultation closes at 4pm on Wednesday, 26 September 2018 and can be emailed to procurement@pharmac.govt.nz

All feedback received by the closing date will be considered by PHARMAC's Board (or its delegate) before making a decision on this proposal.

Kind Regards

Marc Haughey | Team Assistant, Operations

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What are the risks of switching lamotrigine brands?

gsk

The story of how a switch affected a New Zealand child*

- What AED brand was your child initially taking?
  - *Lamictal*
- Was your child's epilepsy under control?
  - Yes
- After the brand switch, how was your child impacted?
  - Impact of the switch was noticed upon weaning. **We chose lamotrigine as it was not supposed to dull her [daughter] down.** When we weaned her, we realised how 'foggy' her brain was on the generic brand. **She was switched to generic very early on and it had the dulling effect on her brain that we had sought hard to avoid.** She had already fought so hard to overcome developmental delays.
  - Upon discussion with her neurologist, it was decided that should she have to go back on lamotrigine, she would only be put on the GSK brand to avoid any potential loss of development.

* Data on file

56% of neurologists reported increased side effects after switching to a generic anti-epileptic drug (AED) brand[1]

Lamictal (LAMOTRIGINE)

What does bioequivalence mean for lamotrigine?

gsk

A study has shown bioequivalent lamotrigine can deviate more than 10% from *Lamictal* in 1 or more pharmacokinetic parameters[2]

These deviations resulted in severe patient consequences in 1/3 of sampled patients, including a break-through seizure and head injury[2]

"Products with a narrow therapeutic index (NTI), such as anticonvulsants are, therefore, not usually considered to be interchangeable[3]" - *Medsafe*

1.Wilner A. *Epilepsy & Behaviour.* 2004;5:995-998. **2.**Nielsen KA et al. *Epilepsy & Behavior.* 2008;13:127-130. **3.**Medsafe. New Zealand Regulatory Guidelines for Medicines [PDF]. The Ministry of Health; 2016. Available at http://www.medsafe.govt.nz/regulatory/Guideline/Part%20D%20-%20NZ%20Regulatory%20Guidelines%20for%20Medicines.pdf

Lamictal® (lamotrigine) is a Prescription Medicine, for adjunctive therapy in the treatment of epilepsy, for partial and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut Syndrome; for the prevention of mood episodes in patients with bipolar disorder, predominately depressive episodes. *Lamictal* is a fully funded medicine without restriction and is available in 2mg, 5mg, 25mg, 50mg and 100mg tablets. **CONTRAINDICATIONS:** hypersensitivity to lamotrigine. **WARNINGS AND PRECAUTIONS:** High initial doses of lamotrigine and exceeding the recommended dose escalation of lamotrigine are associated with adverse skin reactions, usually within the first 8 weeks after initiation of lamotrigine (*Lamictal*) treatment. These have included potentially life-threatening rashes such as Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). Evaluate any patient developing rash; withdraw lamotrigine unless it is clearly not drug related. Abrupt withdrawal may provoke rebound seizures. Possible interference with folate metabolism during long term use. Caution in severe renal failure; not recommended in significant hepatic impairment; monitor patients for signs of suicidal ideation or behaviour; monitor bipolar patients for clinical worsening. **ADVERSE EFFECTS:** Common: Headaches, tiredness, rash (usually maculopapular), aggression, irritability, somnolence, ataxia, dizziness, nystagmus, tremor, insomnia, diplopia, blurred vision, nausea, vomiting, diarrhoea, agitation, arthralgia, pain and back pain. Rarely: conjunctivitis, serious potentially life-threatening skin rashes, including Steven Johnson Syndrome and toxic epidermal necrolysis (Lyell Syndrome). Very rarely: haematological disorders, lymphadenopathy, hypersensitivity syndrome, tics, hallucinations, confusion, aseptic meningitis, worsening of Parkinson's disease, hepatic dysfunction, hepatic failure and lupus-like reactions. Before prescribing *Lamictal*, please review the Data Sheet at www.medsafe.govt.nz. *Lamictal* is a registered trade mark of the GlaxoSmithKline group of companies. Marketed by GlaxoSmithKline NZ Limited, Auckland. **Adverse events involving GlaxoSmithKline products should be reported to GSK Medical Information on 0800 808 500.** TAPS DA1730JB/17DEC/LTG/0009/17a. GSK00595

Angeliqe Nel

From: John Smith <[redacted]
Sent: Thursday, 6 September 2018 11:06 PM
To: Procurement
Subject: Feedback: Proposal to move to one funded brand of lamotrigine
Attachments: 6994996241363225081.jpg; 2665807552707088158.jpg

I support the proposal to switch the funded brand to Logem.

I work in a big pharmacy and we switched all our patients from other brands of lamotrigine to Logem brand with no issue as logem is offered at a 50% discount. We probably switched 30 people and only one came back as she didn't like the taste.

Only problem I see is GSK being sneaky by using a medsafe quote out of context and a case study that makes no sense in marketing material (see attached). This was distributed to pharmacies and probably doctors so this will have to be clearly addressed if proposal was to go through as it left a lot of people confused about generic substitution of this medicine. Lamotrigine has a long half life, good absorption, 1st order kinetics, low first pass metabolism and wide therapeutic range so there was absolutely no reason for GSK to do this if you look at pharmacokinetic properties. This will have to be clearly addressed to health care professionals so they are clear that it is absolutely fine to substitute and to ignore previous lamactal marketing.

MEDICINES UTILISATION SERVICE
Department of Clinical Pharmacology
Christchurch Hospital
PO Box 4710, Christchurch
e: medicines@cdhb.health.nz
t: 03 364 1858

26th August 2018

PHARMAC
PO Box 10 254
Wellington 6143
e: procurement@pharmac.govt.nz

RE: Proposal to move to one funded brand of lamotrigine (Logem) **Due 26th August 2018**

Summary of proposal
PHARMAC is seeking feedback on a proposed change to the funding of lamotrigine dispersible tablets used in the treatment of epilepsy and/or bipolar disorder. Currently, the funded brands of lamotrigine 25 mg, 50 mg and 100 mg dispersible tablets are Lamictal, Arrow-Lamotrigine and Logem. From 1 May 2019, Logem would be the only funded brand of lamotrigine 25 mg, 50 mg and 100 mg dispersible tablets in both the community and hospital settings.

This proposal does not include the 2mg and 5mg dispersible tablets. No change to the brand, listing or funding will occur for these tablet strengths.

CDHB response:

Benefit: Within the CDHB hospitals, an effort is currently made to provide inpatient's their usual brand of lamotrigine, particularly in patients prescribed lamotrigine for epilepsy. One funded brand will reduce the need for this work flow.

Harm: We note that available data suggests there is minor pharmacokinetic variation between lamotrigine dispersible tablet brands. While studies comparing the specific brands available in New Zealand were not found, overall, data suggest harm is unlikely due to pharmaceutic or pharmacokinetic variation.
Harm may arise due to patient medicine management, associated with a change of tablet presentation. This change will require additional input from clinicians and support services to mitigate possible harm in vulnerable patient groups.

Use: CDHB community dispensing data (July 2015 to March 2018) shows 1,625 patients were dispensed lamotrigine (cost $1,943 per patient; approximately $700 per patient per year).
CDHB hospital dispensing data (July 2016 to June 2017) shows 18,217 units of lamotrigine were dispensed (total cost $14,535).

Response from departments: The Mental Health Service, Medicine Information Services, Clinical Pharmacology and Pharmacy Departments, have provided this response.

Regards,

Judy Dalrymple | Medicine Utilisation Pharmacist
Matthew Doogue | Clinical Pharmacologist

Angeliqe Nel

From: Anna Stove <[redacted]
Sent: Wednesday, 19 September 2018 5:40 PM
To: D.Clark@ministers.govt.nz
Cc: Pharmaceutical Society, Richard Townley; [redacted]; Sarah Fitt; Louisa Wall; [redacted]
Subject: Potential risk to patients living with epilepsy that will be required to switch their lamotrigine medications should PHARMAC's proposal be adopted
Attachments: GSK Lamotrigine Consultation Letter to PHARMAC - 19 Sep 2018.pdf

Importance: High

Categories: To file

Dear Minister Clark,

In respect of transparency, I am cc'ing you into our PHARMAC public consultation submission (*attached*).

GSK has significant safety concerns for patients living with epilepsy that will be required to switch their lamotrigine medications should PHARMAC's proposal be adopted.

- There are currently over 10,000 people on lamotrigine in New Zealand and we estimate that 90% of lamotrigine users will be required to switch brands of lamotrigine under PHARMAC's proposal.
- People with epilepsy can live relatively normal lives when seizure control is obtained. However, switching brands of lamotrigine in people living with epilepsy needs to be approached cautiously due to the increased risks of losing seizure control.
- A single seizure can be devastating. It may result in loss of a drivers' licence and has been associated with potential difficulties in employment as well as an increased risk of social isolation, anxiety, depression, injury, suicide and death.
- It can be expected that approximately one-in-four people who switch brands of lamotrigine may require switch-back to the original brand, an option that will not be available under PHARMAC's proposal for sole supply.

As public consultation finishes Wednesday 26th September, please can I request that you review PHARMAC's proposal which is a potential risk to a very vulnerable group of patients living with Epilepsy.

Regards

Anna Stove
General Manager NZ
Community Partnerships Director - Asia Pacific

GSK
[redacted]
Mobile [redacted]
(GlaxoSmithKline NZ Limited Co.No1235481)

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19 September 2018

Lisa Williams,

Director of Operations

C/- Alexander Rodgers

PHARMAC

Dear Lisa

GSK NZ has significant safety concerns for people with epilepsy that will be required to switch their lamotrigine medications should PHARMAC's proposal for one funded brand of lamotrigine be adopted

In response to PHARMAC's call for feedback on the proposed change from three funded brands of 25mg, 50mg and 100mg lamotrigine tablets to just one funded branded of lamotrigine (Logem) (**Proposal**), GSK NZ strongly disagrees with the Proposal and urges PHARMAC to consider the safety concerns highlighted by GSK in the attached submission.

GSK NZ has undertaken a detailed review of the current literature and recommendations from international bodies regarding the potential impact on people with epilepsy when switching brands of lamotrigine. This review along with relevant references are detailed in GSK's attached submission.

The summary of safety concern are as follows:

- There are currently over 10,000 people on lamotrigine in New Zealand and we estimate that 90% of lamotrigine users will be required to switch brands of lamotrigine under PHARMAC's Proposal.
- *Switching brands of lamotrigine in people living with epilepsy needs to be approached cautiously.* Case reports in Canada have previously highlighted increased risks of losing seizure control when people with epilepsy were switched to generic lamotrigine (Makus & McCormick, 2007).
- People with epilepsy can live relatively normal lives when seizure control is obtained. But *a single seizure can be devastating. In some cases, seizure can result in loss of*

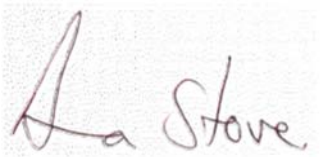
a drivers' licence and has been associated with potential difficulties in employment as well as an increased risk of social isolation, anxiety, depression, injury, suicide and death (Baker, et al., 2001; Bell, et al., 2009; Morgan, et al., 2000; O'Donoghue, et al., 1999; Bell, et al., 2008; Buck, et al., 1997; Hesdorffer, et al., 2012).

- *Widespread brand switching of antiepileptic drugs (AEDs) is not recommended by the majority of international bodies*. International guidelines recommend that people with epilepsy who are seizure free should not switch brands due to the risk of loss of seizure control or emergence of side effects. (G Kramer, 2007).
- Based on retrospective research in Canada and New Zealand, it can be expected that *approximately one-in-four* (Lessing, et al., 2014) *people who switch brands of lamotrigine may require switch-back* to the original brand, an option that will not be as accessible to patients should the Proposal be adopted (Lessing, et al., 2014; LeLorier J, 2008; Andermann, et al., 2007).

GSK NZ believes the Proposal is not in the interests of people with epilepsy who are currently free from seizures. GSK NZ urges PHARMAC to take further consideration of the safety risks.

GSK NZ is willing to work with PHARMAC to find potential solutions to reduce this patient risk. We are open and ready for discussion with PHARMAC. Please find attached a copy of our full submission along with all relevant supporting references.

Yours sincerely



Anna Stove

General Manager

GSK NZ

CC

David Clark, Minister of Health

Louisa Wall, Chair Health Select Committee

Sarah Fitt, CEO of PHARMAC

Graeme Ambler, CEO of Epilepsy Association of NZ Inc.

Richard Townley, CEO of Pharmaceutical Society of New Zealand

GSK RESPONSE TO PHARMAC CONSULTATION
SOLE SUPPLY OF LAMOTRIGINE IN NZ

19 SEPTEMBER 2018

Executive Summary

PHARMAC is seeking feedback on its proposed change to the funding on lamotrigine 25mg, 50mg and 100mg dispersible tablets from three funded brands (Lamictal, Arrow-Lamotrigine and Logem) to just one funded brand (Logem), effective 1 May 2019 in both the community and hospital setting (Proposal).

GSK NZ has significant safety concerns for people with epilepsy that will be required to switch their lamotrigine medications should PHARMAC's proposal for one funded brand of lamotrigine be adopted.

GSK NZ strongly disagrees with the Proposal. The Proposal has the potential to place people with epilepsy at risk of increased breakthrough seizures with significant health and social consequences for these individuals.

It is our understanding that there are currently over 10,000 people currently being prescribed lamotrigine in New Zealand and we estimate 90% of lamotrigine users will be required to switch brands of lamotrigine under the Proposal.

Switching brands of lamotrigine in people with epilepsy who are currently seizure free may have the potential to cause seizures. Widespread brand switching of antiepileptic drugs (**AEDs**) is not recommended by the majority of international bodies. International guidelines recommend that people with epilepsy who are seizure free should not switch brands due to the risk of loss of seizure control or emergence of side effects (G Kramer, 2007).

People with epilepsy can live relatively normal lives when seizure control is obtained. A single seizure can be devastating and can be associated with a significant psychosocial burdens (Baker, 2002). In some cases, seizures may result in loss of a drivers' licence and has been associated with potential difficulties in employment as well as an increased risk of social isolation, anxiety, depression, injury, suicide and death (Baker, et al., 2001; Bell, et al., 2009; Morgan, et al., 2000; O'Donoghue, et al., 1999; Bell, et al., 2008; Buck, et al., 1997; Hesdorffer, et al., 2012).

Based on retrospective research in Canada and New Zealand, it can be expected that approximately one-in-four (Lessing, et al., 2014) people with epilepsy who switch brands of lamotrigine may require switch-back to their original brand (Lessing, et al., 2014; LeLorier J, 2008; Andermann, et al., 2007). This switch-back rate is much higher than those observed with brand switching of statins for cholesterol or even SSRI antidepressants (Andermann, et al., 2007). Under the Proposal, the option of switch-back may not be possible for patients.

Based on the evidence reviewed, GSK NZ believes this Proposal is not in the interests of people with epilepsy who are currently free from seizures who will be required to switch their medications. GSK NZ urges PHARMAC to take further consideration of the risks to safety.

GSK NZ is willing to work with PHARMAC to find solutions and we are open and ready for discussion.

Approximately 90% of people using lamotrigine will be required to switch lamotrigine brands under the Proposal

Lamotrigine is indicated for the prevention of the occurrence of seizures and for the prevention of mood episodes in people with bipolar disorder, predominantly by preventing depressive episodes. It is generally believed that the majority of people using lamotrigine, use it for the treatment of epilepsy, with at least 70% of lamotrigine participants in a New Zealand study using multiple AEDs (Lessing, et al., 2014).

Three brands of lamotrigine have been available in New Zealand for over 10 years (Lamictal, Arrow-Lamotrigine and Logem). Based on dispensing data from PHARMAC, there are over 10,000 people currently undergoing treatment with lamotrigine (Table 1). Based on market share data supplied by PHARMAC under RFP, we calculate that 90% of users of lamotrigine will therefore be required to switch brands of lamotrigine should the Proposal be adopted.

Table 1. Number of people who received a dispensing of the pharmaceutical product as a named person from a pharmacy at least once during the year, as an initial dispensing or all at once (excludes people who only received a repeat dispensing during the year).

DataPharm (beta)

Type	ChemID	Chemical	DHB	YearDisp	NumPharms	NumPpl	NHIComp
Prescriptions	1002	Lamotrigine	New Zealand	2012	39912	8212	98.7
Prescriptions	1002	Lamotrigine	New Zealand	2013	43136	8922	99.1
Prescriptions	1002	Lamotrigine	New Zealand	2014	46049	9659	99.4
Prescriptions	1002	Lamotrigine	New Zealand	2015	48539	10152	99.7
Prescriptions	1002	Lamotrigine	New Zealand	2016	52234	10871	99.7

Potential consequences for people with epilepsy from switching brands

Loss of seizure control when switching brands of AEDs

Switching brands of AEDs may lead to poor clinical outcomes with a risk of adverse events and increased seizure frequency (Chaluvadi, et al., 2011; Privitera MD, 2008).

More than two-thirds (196 of 289 (67.8%)) of US neurologists that responded to a short survey (designed to assess the effects of generic substitution of AEDs), reported breakthrough seizures and more than half (163 of 291 (56%)) reported increased side effects due to generic substitution of AEDs (Wilner, 2004).

Failure of seizure control or drug related adverse effects can have a major impact on quality of life (Baker , et al., 1997). A single seizure can be devastating and can be associated with a significant psychosocial burden (Baker, 2002) including losing one's drivers' licence, difficulties in employment and increased risk of suicide, injury and death (Baker, et al., 2001; Bell, et al., 2009; Buck, et al., 1997; Morgan, et al., 2000; Bell, et al., 2008; Hesdorffer, et al., 2012).

25% of people with epilepsy require switch back to their original brand

Not only does the switching of AEDs lead to a potential loss of seizure control with serious consequences, but studies have shown that when switching brands of lamotrigine, a significant number of people require "switch-back" to their original brand. Under the Proposal there will be no option for switch-back for most of these people.

To better understand the clinical consequence of brand switch of lamotrigine, a published Canadian study (LeLorier J, 2008) found that there was a higher rate (27.5%) of switch-back to the previously used brand of lamotrigine. The author also observed that switching brand of lamotrigine was associated with a significant increase in physician visits and hospital length of stay.

A New Zealand-based retrospective study (Lessing, et al., 2014) evaluated lamotrigine switch between periods of 2005 to 2008 when PHARMAC introduced alternative brands of lamotrigine. The study showed similar switch-back results to LeLorier (2008), with approximately 25% of people switching back to their original brand. This study did not see a significant change in healthcare costs when the original switch was made, nor did it report specifically on why the switch back was required.

It is important to note that the high proportion of switch-back found in both studies (LeLorier J, 2008; Lessing, et al., 2014) may indicate a negative individual acceptance to the brand switch.

Another Canadian study (Andermann, et al., 2007) also looked at switch-back rates between AEDs (including lamotrigine) and other genericised medicines, such as statins (cholesterol lowering) and SSRIs (antidepressants). The study found that switch-back rates for statins and SSRIs are between 1.5-2.9%. AEDs are much higher – between 12-20% and lamotrigine had a switch-back rate of 12.9%.

The results from these studies reflect that people with epilepsy have poor acceptance when their brand of lamotrigine is switched and it is considerably more problematic than other products such as statins and SSRIs where brand changes occur. Although none of the above-mentioned studies explore the reasons for switch-back, it may indicate toxicity and at worst, loss of seizure control (Andermann, et al., 2007).

Reports of loss of seizure control in people with epilepsy due to a brand switch of lamotrigine

A small case-series investigation (Makus & McCormick, 2007) on adverse reactions occurring due to brand switch of lamotrigine was conducted by surveying pharmacists and physicians in Canada. Of the 14 adverse-reaction forms filled out by pharmacists that

responded to the survey used in the study, 11 of the cases (79%) involved loss of seizure control while on another brand of lamotrigine. Of the 9 cases reported by physicians (neurologists and primary care), 8 cases reported loss of seizure control and switched back to the original brand of lamotrigine.

Based on these published reports and the evidence from Canada and New Zealand, GSK NZ draws the conclusion that:

- Approximately one-in-four (Lessing, et al., 2014) people who switch brands of lamotrigine may require switch-back to the original brand, an option that will not be available under the Proposal for sole supply
- Switching brands of AEDs (including lamotrigine) is very different to statins or SSRI antidepressants and has a higher switch-back rate (1.5%-2.9% compared to 12.9%) (Andermann, et al., 2007).
- Loss of seizure control due to brand switch of lamotrigine is a documented risk in people with epilepsy, having consequences beyond the seizure (Makus & McCormick, 2007).
- There is also a potential for higher healthcare utilisation in switching brands of lamotrigine (LeLorier J, 2008).

No alternative supply under a sole supply arrangement

Firstly, sole supply of lamotrigine would not provide an alternative switch-back for people with epilepsy, as outlined previously.

Secondly, there is no in-stock alternative readily available should supply into New Zealand be disrupted with the sole supplier. This would lead to increased seizure risk as people with epilepsy should never be abruptly withdrawn from AED. With multiple different suppliers the risk of an out of stock situation occurring and the abrupt withdrawal of AEDs from treatment, can be mitigated.

Bioequivalence is not always the sole predictor of safety

Bioequivalence is based on the rate and extent to which a therapeutic ingredient is absorbed from a drug in healthy volunteers (Medsafe, 2013). It is not a measure of whether the clinical outcomes such as maintenance of seizure control, are equivalent. The established range for a generic drug to be considered “bioequivalent” is when the pharmacokinetic parameters are 80-125% of the branded drug[1]. (Medsafe, 2013). While this is a well-established range, in AEDs, such as lamotrigine, the relationship between blood levels and seizure control or emergence of side effects is not clearly established (G Kramer, 2007). Therefore, it is not

[1] Bioequivalence exists when the 90% confidence intervals of the ratio (generic compound to reference compound) of GM (geometric means) of pharmacokinetic parameters AUC (Area under the curve) and Cmax (maximum concentration in the blood) fall within the range 80%– 125%. GM is obtained by log transformation of the data.

possible to definitively predict safety of brand switch and will not determine an individual's likelihood to remaining seizure free.

Three recent US randomised controlled studies done in collaboration with the American Epilepsy Society, the Epilepsy Foundation and the US Food and Drug Administration (FDA) (Ting, et al., 2015; Privitera , et al., 2016; Berg M, 2017) demonstrated that different brands of lamotrigine within bioequivalence standards set by the FDA, were bioequivalent in people with epilepsy. However, the studies were not designed or powered to evaluate safety outcomes, such as seizure control, from brand switch. In particular, in one study there was a reported signal of increased seizures in people who switched to generic lamotrigine (Ting, et al., 2015). Therefore, bioequivalence alone in some drug classes may not be sufficient to predict safety. Below is a summary of the abovementioned studies:

Ting 2015 (Ting, et al., 2015) was a bioequivalence study comparing branded lamotrigine to generic lamotrigine in generic brittle[2] people. Although the study demonstrated bioequivalence, there was an increase in loss of seizure control in people who were switched to generic lamotrigine from branded lamotrigine. Total seizures in the Intent To Treat (ITT) population (without subject 026) (n=34) were 49 in the branded arm and 54 in the generic arm (an increase of approximately 9%). Subject 026 had 267 seizures (72% of all the seizures in the study), with more seizures associated with the generic dosing than the branded dosing (ie 208 vs 59, respectively). The author could not find an association between blood concentration of lamotrigine and seizure frequency, further demonstrating that bioequivalence may not be a predictor of safety.

While Privitera 2016 (Privitera , et al., 2016) was of robust design and demonstrated different generic brands of lamotrigine were bioequivalent in people with epilepsy (n=33), the study was not sufficiently powered to detect a difference in seizure control. Furthermore, people who had a history of sensitivities to generic products were unlikely to volunteer for the study and only a small proportion of people (4 (12%) of 33) were considered generic brittle.

Berg 2017 (Berg M, 2017) evaluated single-dose pharmacokinetic bioequivalence of three (one branded and two generic) lamotrigine products in 49 people with epilepsy. The lamotrigine dose that was trialled was 25mg, which is much lower than the normal lamotrigine dose in adults with epilepsy. The subjects included in the study were not dependent on lamotrigine for seizure control (excluded anyone who took lamotrigine within the last 4 weeks). Although the study demonstrated bioequivalence, it was not designed to evaluate safety of brand switch.

Universal switch and sole supply of lamotrigine is against international guidance

Guidelines and position statements have been published by professional bodies in several countries to provide a safe and satisfactory framework for generic substitution of AEDs (see

[2] Generic brittle is defined as having a potential problem with generic switching by virtue of one of the following 1. A history of reported prior exacerbation of seizure or side effects following AED formulation changes; 2. Intolerable AED side effects within the last year prior to the study; or 3. Refractory seizures within the last year prior to study (Ting, et al., 2015).

Table 2) (G Kramer, 2007). The Proposal goes against the majority of international recommendations which discourage widespread substitution of AEDs.

The American Epilepsy Society (AES) acknowledges that AED brand switch with FDA-approved, bioequivalent generic products helps reduce cost and does not compromise efficacy, however, this is the only organisation of note with such recommendations.

Further consideration is required of the potential risks to the safety of people with epilepsy

GSK NZ has undertaken a detailed review of the current literature associated with the Proposal and has significant safety concerns for people with epilepsy that will be required to switch their lamotrigine medications should PHARMAC's proposal for one funded brand of lamotrigine be adopted

GSK NZ strongly disagrees with the Proposal. The Proposal has the potential to place people with epilepsy at risk of increased breakthrough seizures with significant health and social consequences for these individuals.

There are currently over 10,000 people on lamotrigine in New Zealand and we estimate 90% of lamotrigine users will be required to switch brands of lamotrigine under the Proposal.

Based on retrospective research in Canada and New Zealand, it can be expected that approximately one-in-four (Lessing, et al., 2014) people with epilepsy who switch brands of lamotrigine may require switch-back to the original brand (Lessing, et al., 2014; LeLorier J, 2008; Andermann, et al., 2007). Furthermore, switching brands of lamotrigine in people with epilepsy who are seizure free may have the potential to cause seizures. Widespread brand switching of antiepileptic drugs (AEDs) is not recommended by the majority of international bodies.

Despite promising bioequivalence studies in the US (Berg M, 2017; Privitera , et al., 2016; Ting, et al., 2015), these studies were not designed to evaluate safety and do not provide substantial evidence to support widespread brand switch.

Based on the evidence reviewed, GSK NZ believes that the Proposal is not in the best interests of people with epilepsy who are currently free from seizures and urges PHARMAC to further consider the safety risks associated with the Proposal.

Table 2. International epilepsy recommendations on brand switch of AEDs.

International Neurology	**Summarised Recommendation on Brand Switch**	**Weblink and date of version**
American Epilepsy Society	When dispensing medications to patients, healthcare professionals should ensure that a bioequivalent FDA-approved generic product is substituted for the brand or another generic AED	https://www.aesnet.org/about_aes/generic-position-statement Adopted 2016 Accessed September 2018
The Epilepsy Foundation US	The Epilepsy Foundation recommends that consent must be obtained from the individual with epilepsy and their physician before any such substitutions are made – to avoid potentially life-threatening seizures.	Epilepsy Foundation. https://www.epilepsy.com/sites/core/files/atoms/files/Medication%20Switching%20Position%20Statement.pdf Accessed September 2018
International League Against Epilepsy (ILAE) Italian Chapter	In patients who achieved complete seizure remission, switching pharmaceutical products is not recommended; In patients treated with a generic, it is preferable to avoid its substitution with products (including other generics) from different manufacturers. Therefore, it is desirable to specify in the prescription the type (producer) of the generic selected and to add that the product should not be substituted. If substitution is necessary, it may be useful to monitor, whenever possible, the plasma levels of the drug;	https://www.ilae.org/files/dmfile/LICEgenericsguidelines_000.pdf (Perucca, et al., 2006)) Accessed September 2018
International League Against Epilepsy (ILAE) French Chapter	Recommends not to substitute by generics (and even more one generic by another) in the treatment of epilepsy without the agreement of the consulting physician, and of the patient, especially in patients with well controlled epilepsy	https://www.ilae.org/files/ilaeGuideline/PositionStatementGenericAEDs-AES-2007.pdf Accessed September 2018
National Institute for Health and Clinical Excellence (NICE)	Consistent supply to the child, young person or adult with epilepsy of a particular manufacturer's AED preparation is recommended.	https://www.nice.org.uk/guidance/conditions-and-diseases/neurological-conditions/epilepsy#panel-pathways. Revised April 2018. Accessed September 2018
Scottish Intercollegiate Guidelines Network (SIGN)	Stable dosing with individual formulations (generic or branded) is less likely to be associated with worsening control than changing formulations of individual drugs. Some studies suggest that changing between formulations may lead to variations in seizure control and increased utilisation of health resources.	http://www.sign.ac.uk/sign-143-diagnosis-and-management-of-epilepsy-in-adults.html Guideline No 143. Revised 2018 Accessed September 2018

	Formulations of AEDs are not interchangeable and generic substitution should not be routinely made.	
British Epilepsy Association (Epilepsy Action)	Patients should get the same version of their epilepsy medicine, whenever possible, every time they pick up a prescription. Having the same version is known as consistency of supply.	https://www.epilepsy.org.uk/info/treatment/generic-prescribing-parallel-importing Accessed September 2018.
Epilepsy Society Australia	Generic preparations of several antiepileptic drugs are available to patients in Australia. Retrospective studies and case reports indicate that there is a small risk of loss of seizure control or toxicity if interchange of generic and innovator antiepileptic drug occurs. Patients with epilepsy should first obtain the advice of their treating doctor before having the preparation of antiepileptic drug interchanged.	http://www.epilepsy-society.org.au/resources/positions-and-guidelines-generic-aeds.asp ESA advice Oct 2008 Accessed September 2018.
Medicines and Healthcare Products Regulatory Agency (MHRA) UK	**Category 1** • For these drugs doctors are advised to ensure that their patient is maintained on a specific manufacturer's product. • The AEDs in this category are: phenytoin, carbamazepine, phenobarbital, primidone **Category 2** • For these drugs the 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 • The AEDs in this category are: valproate, **lamotrigine**, perampanel, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, topiramate **Category 3** • For these drugs it is usually unnecessary to ensure that patients are maintained on a specific manufacturer's product unless there are specific concerns such as patient anxiety, and risk of confusion or dosing errors. • The AEDs in this category are: levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin	https://www.gov.uk/drug-safety-update/antiepileptic-drugs-updated-advice-on-switching-between-different-manufacturers-products Published November 2017 Accessed September 2018

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Tuesday, 25th September 2018

PHARMAC
Level 9 Simpl House
40 Mercer Street
Wellington Central
By email: procurement@pharmac.govt.nz

Re: Proposal to move to one funded brand of lamotrigine (Logem®)

We have the following feedback on the proposed change to the funding of lamotrigine dispersible tablets used in the treatment of epilepsy and/or bipolar disorder:

Switching to a different AED can frighten epilepsy patients and their caregivers and affect seizure control. Breakthrough seizures can be life threatening.[1]

Seizure control is crucial to patients who have epilepsy. While many think of seizure as just the event—the seizure—and the potential for patient injury, they forget about the later and socially devastating consequences. Patients may lose their driving privileges or employment or suffer from anxiety, depression, or low self-esteem. Clinicians also need to remember that if the sole impact of switching is increased adverse events, the impact can be as burdensome as having a seizure. Adverse events can lead to hospitalization, discomfort, and work or school absences.[1,2]

We note that PHARMAC is quoted in Pharmacy Today -

'The choice of Logem® as the potential sole supply is based on suitability, safety and cost,'

Therefore, in the first instance, it is useful to consider each of these factors in turn.

Cost

We note that PHARMAC has chosen not to publish the pricing for Logem® under the proposed supply arrangement thereby not providing an opportunity for timely comment on the proposed price until after the consultation and decision has been made.

As a government agency PHARMAC has an obligation to ensure its procurement conduct is at all times fair, ethical, transparent and probity rich. We consider this lacks the required probity for a sole supply decision of this magnitude.

We note the opinion of the ombudsman from 14th December 2012 - *I also consider that there is a strong public interest in openness and transparency when developing PHARMAC funding decisions.*

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We note that PHARMAC chose the Enlafax® brand of venlafaxine at a price higher than was offered for Arrow-venlafaxine, with PHARMAC's choice of supplier adding well in excess of $500,000 to the proposed acquisition cost in comparison to Arrow-venlafaxine over the sole supply period. PHARMAC's subsequent communication to the market then lacked transparency on this matter.

Teva (at that time Actavis) communicated with PHARMAC on this matter. (Appendix 1 – communication from Actavis to PHARMAC, names redacted, dated 30th August 2017).

Not publishing the price for Logem® puts the market and in particular current suppliers at a disadvantage in being able to respond in a timely manner and prior to a decision being taken by PHARMAC's board or under delegated authority.

Suitability

There can be little doubt that the most suitable product for those persons currently prescribed lamotrigine in NZ is the brand they and their clinician are currently happy with and which they are settled on.

Logem® cannot be considered more suitable as a sole supply lamotrigine than either Arrow® lamotrigine or Lamictal® and it may certainly be considered as less suitable for a number of reasons, namely –

- Logem® is the least commonly prescribed and dispensed lamotrigine in NZ. (See appendix 2)

- Logem® has no suitable dose form registered for paediatric or other patients who require a dose of less than 25mg. Both Teva and GSK have 2mg and 5mg forms registered.

- Logem® has no comparative bioequivalence data vs Arrow® lamotrigine and there can be no claim of bioequivalence made vs. Arrow® lamotrigine.

Generic-to-generic switching may also produce clinically important differences that may result in seizures.[3] For example, if a patient switches from a generic that is 5% less bioavailable than the brand to a generic that is 5% more bioavailable than the brand - the drugs will differ in bioavailability by 10%.[1] How much the difference of 10% makes will depend on the particular patient, for those who have mild epilepsy they may not notice the change, for those who are fragile or barely controlled the consequences may be catastrophic.

- Logem® has a different excipient profile to both Arrow® lamotrigine and Lamictal®.

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- Logem® utilises a different lamotrigine active pharmaceutical ingredient (API) supplier from those used by Lamictal® and Arrow®-lamotrigine.

One must assume that in the majority of cases the most suitable lamotrigine for those on Lamictal® will be Lamictal®, for those on Arrow® lamotrigine will be Arrow® lamotrigine and indeed for those on Logem® it will by Logem®.

Safety

Logem® may not be considered safer as a sole supply lamotrigine than either Arrow® lamotrigine or Lamictal® as Logem® is the least commonly prescribed and dispensed lamotrigine in NZ.

There can be little debate that the safest product for those persons currently prescribed lamotrigine in NZ is the current brand which the patient being treated with lamotrigine is settled on.

Patients have been prescribed and dispensed both Lamictal® and Arrow® lamotrigine for many years during which time there have been no supply or quality issues with Arrow® lamotrigine.

We are unaware of any supply or quality issues with Lamictal® from GSK.

We note the then Medical Director of PHARMAC's communication in 2007 regarding the listing of Arrow® lamotrigine amongst other products.

'..If a prescriber prescribes generically, the pharmacist may dispense any brand of the pharmaceutical, although it would be prudent to dispense any repeats using the same brand as initially dispensed off the original prescription. Pharmacists should take particular care to ensure that prescribers are aware of brand switching in patients with epilepsy.'[4]

The National Clinical Institute in the UK via https://www.nice.org.uk/guidance/cg137 states that

Consistent supply to the child, young person or adult with epilepsy of a particular manufacturer's AED preparation is recommended, unless the prescriber, in consultation with the child, young person, adult and their family and/or carers as appropriate, considers that this is not a concern. Different preparations of some AEDs may vary in bioavailability or pharmacokinetic profiles and care needs to be taken to avoid reduced effect or excessive side effects.

Consult the summary of product characteristics (SPC) and British national formulary (BNF) on the bioavailability and pharmacokinetic profiles of individual AEDs, ***but note that these do not give information on comparing bioavailability of different generic preparations.***

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As noted by PTAC's Neurology Subcommittee, the Medicines & Healthcare products Regulatory Agency (MHRA) in the UK issued advice regarding brand switching of AEDs, categorising AEDs to help healthcare professionals decide whether it is necessary to maintain a patient on a specific manufacturer's product;

Their advice was as follows:

- Category 1: phenytoin, carbamazepine, phenobarbital, primidone:

Doctors are advised to ensure their patient is maintained on a specific manufacturer's product.

- Category 2: sodium valproate, **lamotrigine**, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, topiramate.

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.

- Category 3: levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin.

It is usually unnecessary to ensure that patients are maintained on specific manufacturer's product unless there are specific concerns such as patient anxiety and risk of confusion or doing errors.

It is important to note that the Neurology subcommittee of PTAC was unable to reach a consensus in relation to lamotrigine; whether it should be in category one or two, or in category two or three.

If one accepts the MHRA advice it cannot be considered in any way safe to enforce switch for the entire patient population being treated with lamotrigine for epilepsy to Logem®.

In the consensus view of The Use of Generic Anti-Epileptics Drugs in Patients with Epilepsy from the United Kingdom Clinical Pharmacists Association (UKCPA): Neurosciences Group & Pharmaceutical Market Support Group (PMSG), patients identified as suitable for switching from brand to generic were summarised as those who agree to try a generic version and are taking an AED which is significantly cheaper as a generic.

Furthermore they must not have any contraindications to switching such as: sensitivity to small dose changes, experience of previous unsuccessful attempts to switch, sustained release preparations, good seizure control, serious consequences from a change in

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seizures (e.g. loss of driving license) and they must not be on a ketogenic diet or have allergies to the excipients in the generic version.

While there is less commentary available regarding switching patients prescribed lamotrigine as a mood stabiliser it is useful to highlight recent sole supply switches in a patient group treated for a similar serious chronic medical condition so as to offer some insight into what may be expected in the enforced switch of patients treated with lamotrigine as a mood stabiliser.

In this regard the funding of Enlafax® XR as the funded sole supply brand for long acting venlafaxine in NZ is instructive.

The sole supply to Enlafax® XR has been plagued by very significant and ongoing reports of lack of efficacy and side effects by a significant number of patients and has even been noted in recent media reports[1].

PHARMAC stated at the time that.

- Enlafax® XR will work in the same way as Arrow®-Venlafaxine XR and Effexor® XR.

- Enlafax® XR 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.

- Enlafax® XR has been thoroughly evaluated by Medsafe to ensure it's safe and works the same as the other brands.

    a. This has not proven to be the case for all those persons who have undergone a brand switch, with Medsafe still reporting[2] numerous instances associated with Enlafax® 12 months after the implementation of sole supply.

That these patient concerns are reflective of real problems can be validated by the large number of patients who continue to purchase both Arrow®-Venlafaxine XR and Effexor® XR.

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[1] https://www.tvnz.co.nz/one-news/new-zealand/patients-wanting-special-funding-antidepressants-turned-down-pharmac

https://www.tvnz.co.nz/one-news/new-zealand/growing-number-patients-questioning-pharmacs-decision-fund-different-brand-anti-depressant

https://www.nzherald.co.nz/nz/news/article.cfm?c_id=1&objectid=12002918

https://www.nzherald.co.nz/lifestyle/news/article.cfm?c_id=6&objectid=11782731

https://www.radionz.co.nz/national/programmes/morningreport/audio/2018663155/supplies-of-preferred-antidepressant-brand-to-run-out

[2] Minutes of the 174th MARC meeting.

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Other issues

Switching of lamotrigine brands currently occurring in NZ

We note that PHARMAC has stated that

'.....many patients taking lamotrigine inadvertently switch between brands, because prescribers usually prescribe the generic drug, not a brand, meaning the patient takes whatever version is stocked in a pharmacy. '

and

In 2017, 60 percent of patients taking lamotrigine had changed brands at some point with no reports of adverse side effects,

We find these claims quite surprising as they in no way reflect Teva's view or experience in the NZ market.

From the volume data for the various lamotrigine brands (Data extract ex Iqvia portal 23rd September 2018 - See Appendix 2) that we have available it appears, on the face of it, implausible that 60% of patients changed brands during 2017.

If PHARMAC does have data to show that 60% of patients did change brands at some stage during 2017 it would be useful to analyse if these patients had any particular characteristics whereby the pharmacist, patients and clinician felt confident in allowing brand switch and conversely why this was not deemed case in the remaining 40% of patients.

We submit that if this data is available to PHARMAC it is quite critical that it is or has been presented to PHARMAC's relevant clinical advisors for their comment.

PHARMAC's comments also paint an unfavourable view of NZ pharmacists, suggesting they dispense whatever brand they have in the pharmacy regardless of clinician or patient's requirements.

This does not reflect Teva's experiences of the pharmacy profession in NZ.

Teva's experience is that the vast majority of pharmacists enquire about the brand the patient usually takes when dealing with products such as anti-epileptic medications, thyroxine, salbutamol inhalers, etc.

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Insufficient consultation

We note that PHARMAC's consultation states that those PHARMAC thinks will be interested in their proposal are –

'People currently using lamotrigine, consumer support organisations for people living with epilepsy or mental health conditions, pharmacists, clinicians involved in the management of bipolar disorder and/or epilepsy, DHBs and suppliers of lamotrigine tablets.'

We note that PHARMAC do not appear to reliably inform patients before, during or after brand switches in any substantive manner apart from posting notification on their website.

We note that PHARMAC has provided little advice during previous consultations regarding what patients should do if they experience issues during brand switches apart from advice such as ..

'you should talk with your doctor, nurse or pharmacist...'

With the potential consequences of breakthrough seizures in previously stable patients having the potential for such deleterious effect on patient's health, independence, lifestyle and ability to drive, we believe there is a particular a duty of care for PHARMAC to go beyond what has been considered acceptable in past consultations with patients and patient groups.

With brand changes which have the potential to deliver potentially deleterious effects on patients we submit that there is an additional duty on the agency enforcing the switch to inform patients what avenues, if any, for redress or relief are available should the brand switch impact on their ability to drive, their employment or in any other way which may cause hardship.

We note that PHARMAC has as a general rule been unwilling to assist patients under the Named Patient Pharmaceutical Assessment scheme (NPPA) in relation to previous brand switches due to fiscal risk if this is to be the case during a lamotrigine brand switch it should be explicitly stated during the consultation.

It may be expected that a number of patients will wish to remain on Arrow®-lamotrigine or Lamictal® post sole supply being awarded to Logem®, we are aware there remain a number of patients purchasing Arrow®-venlafaxine and Effexor® despite there being no funding available from PHARMAC.

There is increasing reliance on the provision of non-reimbursed products – to underwrite PHARMAC's sole supply activities for those who are unable to tolerate the sole supply brand.

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While patients remaining on non-funded products may be fiscally beneficial to PHARMAC and indeed may be part of PHARMAC's strategy to decrease public expenditure it does mean there are serious questions of equity between those patients who are able to afford to continue on their preferred medication and those who, for financial reasons, are forced to switch to a new brand.

Transition period

We note that PHARMAC is currently consulting on another proposal that would simplify the transition period for changes made to community medicines by removing the referencing pricing period during brand changes.

With the expected benefits that:

- Wholesalers would be less likely to be left with excess stock at the end of the transition period as both brands would be listed with full subsidy for longer.
- Suppliers would be less likely to experience losses through left-over stock at the end of the transition, as currently they must account for how much of the market will continue to use their product during the second transition period (during reference pricing).
- Patients and pharmacies would no longer need to cover the residual cost of continuing use of the outgoing brand during reference pricing and would be less likely to have left over stock at the end of the transition period.

We find it contradictory that in this current consultation PHARMAC suggests that those brands that have not been chosen by PHARMAC for sole supply will likely have a period of no more than 2 – 3 months prior to having to reduce price or having a part charge applied.

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Low dose lamotrigine

We note that PHARMAC has stated that -

This proposal would not affect the currently listed lamotrigine 2 mg and 5 mg dispersible tablet presentations, which are mainly used in children.

We can confirm that should the consultation be approved in its current form Teva will withdraw Arrow®-lamotrigine 5mg from supply along with other strengths of Arrow®-lamotrigine as current stock in our warehouse is depleted.

Decreased competition in the market

We note the potential risk when approving sole supply for products treating relatively fragile conditions such as epilepsy, certain mental health conditions and transplant medicines that there may be little if any willingness to change the patient base multiple times, effectively providing the initial successful supplier with supply of their product in close to perpetuity.

While PHARMAC has specific exemptions under the Commerce Act we believe such a decrease in competition would have a deleterious effect on the NZ pharmaceutical industry and is not an intended consequence of the exemption.

We note that PHARMAC has chosen Mylan as its preferred supplier in both cases despite both Arrow®-lamotrigine and Arrow®-venlafaxine being used by very significantly more patients than Mylan's products and Mylan's imperfect supply performance over recent times with various medications.

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Confidentiality

We understand that this feedback will be considered by PHARMAC's Board (or its delegate) prior to making a decision and that this document is subject to the Official Information Act 1982.

Should any request be received for the information contained in this communication Teva does not consider that any information contained herein is commercially sensitive and no information should be withheld or redacted by PHARMAC or its agents, excepting where there is a requirement to protect the privacy of a natural person.

Sincerely
Teva Pharma (New Zealand) Ltd

John Wickens

References

1. Garnett WR. Switching AED formulations: defining the issues. *Adv. Stud Pharm*. 2008;5:140-145.

2. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: cause for concern? *Epilepsia*. 2013;54:11-27.

3 .Zachry WM, Doan QD, Caldwell JD, Smith BJ. Case-control analysis of ambulance, emergency room, or inpatient hospital events for epilepsy and antiepileptic drug formulation changes. *Epilepsia*. 2009;50:493-500.

4. PHARMAC communication to General Practice – Jan 2007 - Listing of generic lamotrigine, risperidone and clozapine (See App. 3)

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Appendix 1:

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New Zealand

PO Box 128244
Remuera
Auckland
New Zealand

30th August 2017

[redacted]
PHARMAC
P.O. Box 10-254
Wellington

By email: procurement@pharmac.govt.nz

Dear [redacted]

Re: Venlafaxine

You state in your letter that -

'The purpose of the consultation process is to seek feedback from interested parties on the possible effects of the proposed amendment to the Schedule – in this case the proposal to list Enlafax XR with sole supply until 30 June 2020.

While submitters are free to raise whatever points they wish to, our consultation process is not intended as an opportunity for commercial parties to seek to re-litigate or review the evaluation component of the procurement process that has led to the proposal.'

As part of this consultation PHARMAC has an obligation to make clear to interested parties, in particular the medical community and affected patients why a decision has been taken to fund a product which will come with a higher acquisition cost than one of the incumbent products. For a person not privy to this information our opinion is that the current consultation serves to both mislead and misinform.

You also state that –

'As we have already reiterated in our email to you on 15 August, the RFT document clearly signaled that there were a wide range of factors which the Evaluation Committee would take into account during its evaluation process.'

PHARMAC has repeatedly failed to expand on these *'wide range of factors'*, we look forward to a more comprehensive and transparent response to our requests under the official information act.

We also note that despite these wide range of factors particular emphasis was to given to those aspects of Tender Bids which demonstrate "health outcomes", and those aspects of Tender Bids which demonstrate the impact on the "funding provided" for pharmaceuticals. The RFT clearly stated that these factors would be given the greatest weight by the Evaluation Committee. We also note that in this instance PHARMAC appears to have ignored their obligations as per the Government Rules of Sourcing.

Sincerely
Actavis New Zealand limited

John Wickens
Business Development Manager

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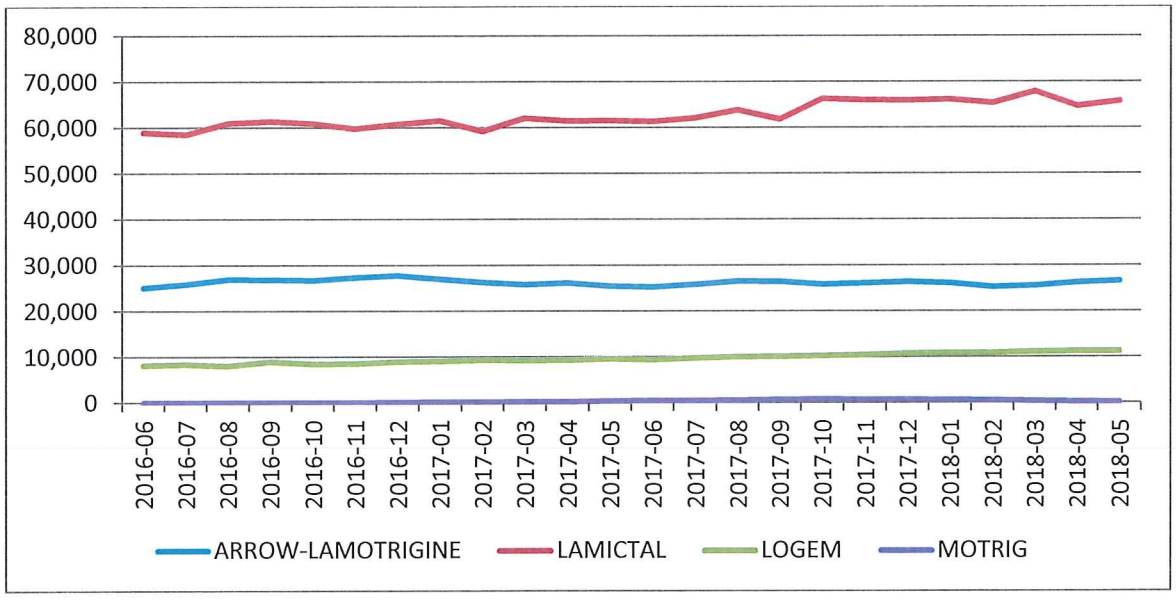
Appendix 2:

Monthly packs of lamotrigine by brand June 2016 – May 2018

Period	ARROW-LAMOTRIGINE	LAMICTAL	LOGEM	MOTRIG
2016-06	25,071	58,976	8,205	-
2016-07	25,819	58,503	8,365	-
2016-08	26,896	61,009	8,072	6
2016-09	26,834	61,400	8,950	15
2016-10	26,659	60,891	8,479	26
2016-11	27,288	59,805	8,555	49
2016-12	27,769	60,795	8,979	68
2017-01	26,965	61,562	9,078	126
2017-02	26,240	59,250	9,320	153
2017-03	25,802	62,125	9,207	200
2017-04	26,120	61,493	9,293	257
2017-05	25,450	61,506	9,575	345
2017-06	25,210	61,299	9,404	425
2017-07	25,769	62,126	9,705	448
2017-08	26,457	63,847	9,995	537
2017-09	26,404	61,813	10,078	655
2017-10	25,758	66,270	10,180	727
2017-11	26,036	65,997	10,436	678
2017-12	26,318	65,956	10,726	636
2018-01	26,068	66,130	10,861	611
2018-02	25,256	65,374	10,809	517
2018-03	25,505	67,905	11,093	370
2018-04	26,167	64,700	11,236	231
2018-05	26,557	65,766	11,262	189



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Appendix 3

10 January 2007

Name of Doctor or Pharmacist
Sample Surgery / Sample Pharmacy
PO Box 12345
SAMPLE CITY

Dear Doctor/Pharmacist

Listing of generic lamotrigine, risperidone and clozapine in the Pharmaceutical Schedule from 1 February 2007

From 1 February 2007, generic lamotrigine, risperidone and clozapine will be listed fully subsidised in the Pharmaceutical Schedule, as follows:

Lamotrigine chewable/dispersible tablets

There will be two brands of generic lamotrigine chewable/dispersible tablets 25 mg, 50 mg, 100 mg and 200 mg:

Mogine (Douglas Pharmaceuticals)

Arrow-Lamotrigine (Arrow Pharmaceuticals)

Arrow-Lamotrigine will also be available in a 5 mg strength.

Both brands of generic lamotrigine will be available fully subsidised without the need for Special Authority application. This will allow widened access for use in patients with bipolar disorder.

Risperidone tablets

Douglas Pharmaceuticals' generic risperidone (Ridal) 0.5 mg, 1 mg, 2 mg, 3 mg and 4 mg tablets will be listed fully funded under the "Retail pharmacy – specialist" restriction that currently applies to the prescribing and dispensing of risperidone.

Clozapine tablets

Two new strengths of Clopine (Douglas Pharmaceuticals' generic clozapine tablets) – 50 mg and 200 mg – will be listed fully funded in addition to the existing listed strengths of Clopine (25 mg and 50 mg). All strengths of Clopine will be listed subject to the "Hospital pharmacy [HP4] – specialist prescription" restriction that currently applies to the prescribing and dispensing of clozapine.

Availability of existing brands of lamotrigine, risperidone and clozapine

The Lamictal (GlaxoSmithKline NZ Ltd) brand of lamotrigine will remain listed under Special Authority for subsidy for patients with epilepsy meeting the criteria.

The Risperdal (Janssen-Cilag Pty Ltd) brand of risperidone tablets will continue to be listed fully subsidised under the same restrictions as currently apply to the prescribing and dispensing of risperidone tablets.

The Clozaril (Novartis NZ Ltd; Sandoz) brand of clozapine will continue to be listed fully subsidised under the same restrictions as currently apply to the prescribing and dispensing of clozapine.

Bioequivalence

Both Douglas Pharmaceuticals and Arrow Pharmaceuticals were required to demonstrate bioequivalence of their products relative to the innovator products as part of the Medsafe registration process. Please find attached to this letter excerpts from the bioequivalence studies reviewed by Medsafe during registration.

Reminder regarding brand switching

Regulation 42(4) of the Medicines Regulations requires a pharmacist to dispense the brand of medicine prescribed. If the prescriber prescribes a medicine by brand name, or by reference to a manufacturer, that brand must be dispensed unless the prescriber has authorised the change. Therefore, if a prescriber wishes a particular brand to be dispensed, this must be specified on the prescription.

If a prescriber prescribes generically, the pharmacist may dispense any brand of the pharmaceutical, although it would be prudent to dispense any repeats using the same brand as that initially dispensed off the original prescription. Pharmacists should take particular care to ensure that prescribers are aware of brand switching in patients with epilepsy.

If you have any questions regarding these changes, please contact the PHARMAC help line on 0800 66 00 50 (weekdays between 9 am and 4 pm).

Yours sincerely

Peter Moodie
Medical Director

MEDSAFE
NEW ZEALAND MEDICINES AND MEDICAL DEVICES SAFETY AUTHORITY
A BUSINESS UNIT OF THE MINISTRY OF HEALTH

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19 September 2018

procurement@pharmac.govt.nz

Dear PHARMAC,

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

I am writing to provide feedback on PHARMAC's proposal to reduce the number of funded brands of lamotrigine from three to one.

Medsafe considers that the proposal goes against the international consensus on switching between brands of anti-epileptic medicines. Medsafe also considers that this proposal poses a potential significant safety issue. The international consensus [1] is that even with bioequivalent anti-epileptic medicines, switching could result in the loss of seizure control for any individual using this medicine to control their epilepsy. A single seizure can be extremely detrimental to a patient's life and all measures should be taken to ensure this risk is minimised. Consensus between international organisations and published literature is that any decision to change brands of AEDs should be made between the prescriber and the patient with approval from a specialist.

In this submission Medsafe would also like to comment on statements noted in the minutes of the Neurological Subcommittee of the PTAC meeting held on 11 November 2015, which has been provided as justification for the proposal.

We note that the minutes from the PTAC meeting on 11 November 2015 state that only funding one brand will reduce the potential for inadvertent brand switches. Although there has been funding for three lamotrigine products, the Centre for Adverse Reactions Monitoring (CARM) has only received seven reports of suspected adverse reactions to a brand switch of lamotrigine. The majority of these cases were reported a long time ago when generic brands were first funded. There is no evidence in the current CARM data that this is an ongoing problem. However, as with other brand switches in the past, a small proportion of patients can be expected to suffer from adverse effects when changing brands. I note, however, that three of the seven reports included *convulsion* as an adverse reaction which supports the international consensus. Even a single seizure in an individual previously well controlled is a significant event and risk minimisation measures should be employed where possible.

There is international consensus that patients with epilepsy controlled by antiepileptic medicines (AEDs), including lamotrigine, should not undergo generic substitution without approval from the consulting specialist and under close clinical supervision. From a clinical perspective, the American Academy of Neurology (AAN) has stated that they oppose generic substitution of AEDs for the treatment of epilepsy without the attending physician's approval. To quote one of the authors of this statement:

> *"Epilepsy is unlike other disorders. The marker for success is whether or not you're having seizures and whether or not you're having side effects. So unlike a condition such as hypertension, where, if you make a change in dose you can monitor blood pressure to determine whether it's working or not, with epilepsy you either have an all-or-nothing phenomenon; you're either seizure free or you're not. Having a breakthrough seizure could*

mean a person could lose their driver's license or their job or injure themselves or someone else. This has to be weighed against the potential cost savings of switching to a generic anticonvulsant".

- *George Barkley MD, AAN*

This position is echoed by international regulators, including the Medicines and Healthcare products Regulatory Agency (MHRA), Food and Drug Administration (FDA) and Swedish Medicinal Products Agency. A number of societies and groups with a vested interest in epilepsy and AED usage, including the National Institute for Health and Care Excellence (NICE), the International League Against Epilepsy (ILAE), the Epilepsy Foundation, and the American Epilepsy Society have also recommended avoiding generic substitutions for antiepileptic medicines, including lamotrigine, due to the risk of seizure reoccurrence. Medsafe agrees with the recommendation that patients with controlled epilepsy should not switch between brands of AED (even when bioequivalent) without input and monitoring from specialists.

As noted in the minutes for the Neurological Subcommittee of PTAC meeting on 11 November 2015, the MHRA have provided a risk-based categorisation of AEDs to assist decision making on switching between different brands. The original advice, published in December 2014, categorised lamotrigine as category 2, whereby the need for continued supply of a particular brand should be based on clinical judgement and consultation with the patient/or carer, taking into account factors such as seizure frequency and treatment history. In 2017, the advice was updated to include consideration of patient-related factors. Other medicines in this category include valproate and topiramate, both of which have either the innovator as sole supply or multiple funded brands. Medsafe concurs with this categorisation. Medsafe notes in the 11 November 2015 meeting minutes that the Subcommittee contests this position in relation to lamotrigine. Medsafe agrees with the advice from the MHRA in this situation.

The published literature contains many references supporting Medsafe's advice on switching AEDs. We note that whilst some of the available literature was considered by the Subcommittee, other important studies were not referred to. Additionally, Medsafe considers that some studies noted by the subcommittee were either not relevant to lamotrigine and/or the current proposal by PHARMAC.

A systematic review by Desmarais et al in 2011 noted that studies have reported higher switch-back rates following generic substitution of AEDs than substitution of other commonly prescribed medicines. Specifically, a switch from Lamictal to generic lamotrigine, has been associated with increases in required dose, increased number of co-prescribed AEDs, more frequent outpatient visits and longer hospitalisations. Although seizure reoccurrence was not a measured outcome, the authors of these studies suspect this to be a factor in the observed increase in medical-service utilisation and longer hospital stays [2].

The Subcommittee considered a systematic review by Kesselheim et al, however none of the studies included lamotrigine. Additionally, the results of the review stated that no randomised controlled trials found that the brand-name AED was superior or inferior to the generic product in controlling seizures. Medsafe has already established the non-inferiority of generic products through its generic medicine approval process. Therefore, the RCTs in this study are of limited relevance to the current proposal as they do not evaluate the action of substitution, only the efficacy of generic products. However, the observational studies of patients with epilepsy who were switched from brand to generic products identified changes in health-service utilisation that the authors concluded may suggest less than adequate seizure control with the generic product [3]. Therefore, this study supports the notion that switching patients from one brand of AED to another may be detrimental to the seizure control for patients taking lamotrigine for epilepsy.

The Subcommittee also considered a systematic review by Yamada et al. The authors of this review concluded that retrospective studies suggested issues with generic substitution of AEDs, while prospective studies suggested it can be safe. The authors call for healthcare professional diligence to minimise the risk of serious treatment failure consequences [4].

Thank you for the opportunity to provide feedback on this proposal. If you would like to discuss this further, please do not hesitate to contact me.

Yours sincerely,

Chris James
Group Manager
Medsafe

1. Atif M, Azeem M and Sarwar MR. 2016. Potential problems and recommendations regarding substitution of generic antiepileptic drugs: a systematic review of literature. *SpringerPlus* 5(1): 182.

2. Desmarais JE, Beauclair L and Margolese HC. 2011. Switching from brand-name to generic psychotropic medications: a literature review. *CNS neuroscience & therapeutics* 17(6): 750-760.

3. Kesselheim AS, Stedman MR, Bubrick EJ, et al. 2010. Seizure outcomes following the use of generic versus brand-name antiepileptic drugs. *Drugs* 70(5): 605-621.

4. Yamada M and Welty TE. 2011. Generic substitution of antiepileptic drugs: a systematic review of prospective and retrospective studies. *Annals of Pharmacotherapy* 45(11): 1406-1415.

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21 November 2018

Sarah Fitt
Chief Executive PHARMAC
by email: [redacted]

Dear Sarah

Clarification of Medsafe's position re potential funding changes for lamotrigine

Thank you for providing Medsafe with the opportunity to clarify our earlier submission to PHARMACs consultation on lamotrigine funding. We note your decision to seek further advice from Medsafe and would also like to clarify our interpretation of the paper stated to be the best evidence of successful switching of lamotrigine.[1]

Medsafe has some concerns regarding this paper.

One of the stated aims of the study is to assess the use of national administrative databases to evaluate health outcomes and potential costs or savings to generic reference pricing in New Zealand. However no validation of the method appears to be reported in the paper. Some of the limitations are discussed but this is not a method validation. The National Minimum Data Set (NMDS) may not be a reliable source of epilepsy-related outcomes, the authors did not appear to explore whether patients with epilepsy who experience a seizure are captured in this dataset.

From a pharmacovigilance perspective the paper is not meaningful, firstly because we do not know that the methodology could detect any difference. Secondly because the power of the study to exclude a level of harm was not discussed. As the outcome was negative from our perspective we would like to know at what frequency level this might represent reassurance. In other words does the study exclude a frequency of harm of 1 in 10 or closer to 1 in 1000? This figure will be relevant to determining the likely cost benefit to the health care system.

In addition the results of this analysis are unlikely to be predictive of events that would occur after a switch to sole supply. In a similar analysis for venlafaxine switching it was also concluded there was no change in health outcomes.[2] However, the current reports

[1] Lessing C, Ashton T, Davis P (2014) 'The impact on health outcomes and healthcare utilisation of switching to generic medicines consequent to reference pricing: The case of lamotrigine in New Zealand' Appl. Health Econ. Health Policy 12: 537-546

[2] Lessing C, Ashton T, Davis P (2015) 'AN evaluation of health service impacts consequent to switching from brand to generic venlafaxine in New Zealand under conditions of price neutrality' Value in Health 18 646-654

to the Centre for Adverse Reactions Monitoring (CARM) regarding venlafaxine suggest that there may have been increased utilisation of healthcare services.

Finally we note that description of bioequivalence in the introduction to this paper is incorrect.

We note during the discussion in our meeting that studies showing adverse effects of switching brands of lamotrigine were dismissed because they were sponsored by pharmaceutical companies. This position is inconsistent with PHARMACs acceptance of pharmaceutical company sponsored biostudies for funding generic medicines. The studies may not have been reliable but that should be concluded after careful analysis, not dismissed based on the funding source for the study alone.

Medsafe notes that the current proposal to change the funding for lamotrigine is based on an analysis that was conducted three years ago. We suggest that a review of the scientific literature since then may reveal additional useful information. For example the results of the EQUIGEN trial published in 2017 concluded that lamotrigine products were bioequivalent in patients with epilepsy.[3] Whereas bioequivalence studies are normally performed in healthy volunteers.

The UK epilepsy society has published a survey on patient experiences of switching anti-epileptics which provides further insight into the problems that patients might experience with a change in funding. Medsafe notes that switching lamotrigine was cited most often by patients in this survey as leading to negative effects. We know that negative perceptions are a major cause of 'brand switch' reactions. If similar perceptions are formed around a lamotrigine we expect to receive a significant number of adverse reaction reports. Each time these events occur patient and healthcare professional trust in the health system is reduced.

Should PHARMAC decide to go ahead with a sole supply tender for lamotrigine Medsafe recommends that affected patients are first reviewed by their GPs. The switch should not occur when the patient reaches the pharmacy without prior counselling by the GP. GPs should also refer the most vulnerable patients for specialist intervention to oversee and monitor the switch.

For patients with epilepsy the most vulnerable people are considered to be those who are seizure free since the impact of a seizure would be profound, and those with labile seizures since any variability could lead to loss of control. We would expect that switching in these patients would need to be managed by a specialist. Therefore the usual time period for switching may need to be extended.

Patients with epilepsy may also have memory problems or learning difficulties therefore a patient leaflet will be needed to help explain in changes in the tablet or dose. This leaflet will need to be readable and understandable by this group of people. Leaflets should be distributed by both GPs, specialists and pharmacists. All patients should be actively followed up to check that they are coping well with the change.

---

[3] Berg M, Welty T, Gidal B et al (2017) "Bioequivalence between generic and branded lamotrigine in people with epilepsy The EQUIGEN randomized clinical trial' JAMA Neurology 74:919-926

For patients taking lamotrigine for other indications switching is generally considered to be less problematic, however this group of patients generally finds change very difficult and will need at least GP level support and monitoring.

Healthcare professionals and patients should be reminded of the symptoms which may indicate a risk of reduced bioavailability and those of increased bioavailability so that urgent review can occur. There appears to be a number of case reports in the literature which may provide information in the absence of advice from PHARMACs event advisory groups. Of particular concern to Medsafe would be a breakthrough seizure, induction of hypersensitivity, QT prolongation and suicidality.

Medsafe notes that these actions to mitigate harm occurring to patients have the potential to significantly increase the cost of healthcare for the patient. PHARMAC should consider ways to mitigate these costs and to actively consider how health equity issues will be addressed. In addition PHARMAC should ensure that an alternative funding mechanism is made more accessible for patients who need to switch back to their original brand.

Yours sincerely

Chris James
Group Manager
Medsafe

CC: Adrienne Martin
Email: [redacted]

PHARMAC
Pharmaceutical Management Agency

FILE NOTE

Subject:	Medsafe consultation feedback on lamotrigine proposal
Event Type:	Meeting
Author:	Adrienne Martin
Attendees:	PHARMAC: Adrienne Martin (Senior Therapeutic Group Manager/Team Leader), Janet Mackay (Manager, Implementation Programmes), Geraldine MacGibbon (Manager, Pharmaceutical Funding), Peter Murray (Deputy Medical Director). Medsafe: Chris James (Group Manager), Jared Solloway (Advisor Pharmacovigilance), Susan Kenyon (Manager, Clinical Risk Management).
Location:	PHARMAC
Date event took place:	13 November 2018

PHARMAC staff met with representatives from Medsafe to discuss its feedback received on 26 September 2018 in response to PHARMAC's 29 August 2019 consultation on a proposal to move to one funded brand of lamotrigine.

PHARMAC staff noted that the proposal is currently on hold while we take time to consider the feedback we have received. PHARMAC staff noted that they had wanted to meet with Medsafe to better understand the issues raised in Medsafe's feedback. PHARMAC staff noted that such meetings commonly occur when issues of significance are raised during consultation and are important to ensure that PHARMAC staff fully understand the issues.

The agenda below was discussed. Important points from the discussion are summarised.

1. Discuss the concerns raised in the Medsafe consultation feedback.

   PHARMAC staff

   - Noted that we had received both supportive and concerned responses at consultation. Patient feedback centred around concerns of seizures as a result of a brand switch and clinician feedback was supportive including support from the NZ branch of the International League against epilepsy.

   - Noted that the Attif et al. 2016, systematic review did not detail an international consensus about brand switching and wanted to understand Medsafes view of this further.

   - Discussed that our interpretation of the feedback from Medsafe was that inadvertent switching (as is currently occurring) would be acceptable; however, a managed switch to one brand would not. Medsafe noted this was misinterpreted by PHARMAC (see point below). We noted that data from the Pharmaceutical Collection indicates that approximately half the funded use of lamotrigine is for epilepsy and that approximately half of the epilepsy patients dispensed lamotrigine in the last year have had at least one brand switch at some point. We assume that a reasonable proportion of this switching is currently occurring in an unmanaged way.

Commented [CJ1]: Medsafe was informed at the meeting that all feedback positive (with the exception of Medsafe's submission)

Commented [CJ2]: We do not recall this being discussed and is new information to Medsafe

- Offered to send Medsafe the dispensing data we have on lamotrigine.
- Noted that we have a number of other RFPs currently open that could involve potential brand changes (eg. etanercept and flecainide) and encouraged Medsafe to let us know as soon as possible if it has a particular view on potential brand switches for these chemicals.

Commented [CJ3]: Medsafe does not consider this point is within scope of this meeting. Please consider removing.

Medsafe staff

- Clarified that ~~there was not~~the use of the term "international consensus" refers to "international regulator consensus" against brand switching of lamotrigine, ~~but there is international regulator consensus against brand switching~~ as per the MHRA's advice on anti-epileptic drugs (AEDs). Medsafe support the MHRA's categorisation of AEDs and advice regarding brand switching for each category.
- Noted that the MHRA advice had been updated since the Neurological Subcommittee meeting. Category 2 advice now includes taking into account patient/carer-related factors such as negative perceptions about alternative products and/or other issues related to the patient should also be taken into account.
- Noted some of the difficulties that patients have experienced with the venlafaxine brand change and highlighted concerns that a change for lamotrigine may cause similar difficulties.
- With regards to PHARMAC's interpretation of Medsafes feedback (that inadvertent switching was acceptable; but a managed switch was not) Medsafe staff clarified that this has been misinterpreted.. Rather, based on the small number of reports received by CARM of "brand switch reactions", there was little evidence of adverse effects due to inadvertent brand switching. This was from a regulatory, pharmacovigilance perspective based on adverse drug reaction reports and not dispensing data. ~~They had been under the impression that switching wasn't happening much now given that there are hardly any reports to CARM (vs several reports when generics were first listed). They were surprised to hear the information we had about switching that is still occurring.~~
- Discussed that although lamotrigine generics are bioequivalent to the innovator, there are always a group of people who experience difficulties with brand changes eg ~~levothyroxine and~~ venlafaxine.

Commented [CJ4]: Levothyroxine was not a brand switch – it was a formulation change. Medsafe made this point at the meeting also.

- Clarified that it did not need to see dispensing data from PHARMAC, but wanted to highlight that it had provided feedback in the absence of data. Suggested that PHARMAC ~~look at its data to see~~should consider ~~how many~~ people ~~are~~ taking both venlafaxine and lamotrigine ~~to help with any implementation if this proposal is to go ahead.~~ who may be primed against brand switching. Medsafe believe this should be taken into account.

2. Discuss the literature cited by Medsafe; our interpretation of this appear to differ.

PHARMAC staff

- Discussed the literature provided by Medsafe and that although there are numerous studies regarding the health outcomes with regards to switching of AEDs, the SC's advice had centred on two particular studies ((Lessing et al. Appl. Health Econ. Health Policy. 2014), (Hartung et al. CNS Drugs. 2012)), one being directly relevant to the NZ population and the other providing information on international experience.

- Noted that the Medsafe letter mentioned that there are other studies that were not referred to by the Neurological SC and that we would appreciate if Medsafe could share these with us as we can then seek the Neurological SC's advice on these particular studies.

Medsafe staff

- Clarified that the cited references were to highlight evidence that did not appear to have been considered by the Neurological Subcommittee, according to the published minutes.
- Clarified that there was one systematic review by Desmarais et al in 2011 that included studies not referenced in the published minutes of the Neurological Subcommittee's meeting.
- ~~Clarified that there was only one other (unpublished, draft manuscript) study that it was aware of and that there were no other important studies as referred to in its letter.~~Noted that the recommendations were made by the Neurological Subcommittee in 2015 and suggested a more current literature review would be useful.
- Noted that they would be happy to share any other research that they came across, from a regulator perspective, that may be useful for PHARMAC and its clinical advisors to consider.

3. Understand how switching of lamotrigine brands differs from the recent phenytoin formulation brand switch, gabapentin switch and a previous formulation change for sodium valproate in 2014.

PHARMAC staff

- Discussed that we are interested in Medsafe's view of what went well with the recent phenytoin formulation change and what, from a regulators perspective, we could do to support a change in funded brand of lamotrigine, if the proposal was to go ahead.
- Said that we would welcome any advice on switching AED from any of Medsafe's international regulator colleagues.

Medsafe staff

- Noted that the phenytoin switch did not involve a change in ~~brands, meaning that patients were not as concerned as they would be with a brand change~~brands, rather it is a formulation change which can't be stopped from happening provided the new formulation meets required manufacturing standards. The change is fully managed by the company who have all necessary data.
- Noted that the phenytoin switch was managed by the supplier and that support was provided ~~by~~ to HCPs to help manage their patients.
- Said that they would look to see if there was any information available from other international regulators to help with switching AEDs and provide it to PHARMAC if available

4. Understand the difference between Narrow Therapeutic Index (NTI) and non-NTI AED

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switching

PHARMAC staff

- Highlighted that we would like to clarify if lamotrigine was a NTI AED and what the difference between switching NTI and non-NTI AEDs is?
- Wanted to understand if Medsafe's views would be different if we were proposing a sole supply arrangement with the Lamictal (innovator) product.

Medsafe staff

- Noted that one difference between switching a non-NTI and a NTI-AED would be that some NTI AEDs can have plasma concentrations measured to help with clinical management.
- Confirmed that lamotrigine is not ~~considered to be~~regulated as an NTI AED but is considered a category 2 AED as per the MHRA's classification. Medsafe notes that measuring the blood concentrations of lamotrigine in individual patients is available in New Zealand, and may be of value before and after the change to aid clinical management of the switch. ~~before and after the change help with clinical management of the switch~~PHARMAC may wish to obtain further expert advice on the value of monitoring lamotrigine concentrations.
- Noted that Medsafe align with the MHRA recommendations for switching of any AEDs.
- Noted that Medsafe considers all generics to be bioequivalent to Lamictal and that it would have the same views if we were proposing a switch from a generic to the Lamictal (innovator) brand.

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