Comments on agenda items for the 63rd meeting of the Medicines Classification Committee to be held on 10 October 2019

Comment received on the agenda for the 63rd meeting of the Medicines Classification Committee

Agenda item:	7.2e Artemisia annua
Submitter:	Cynthia Hunefeld Clinical researcher, Clinical Herbalist and natural products formulator

Has it been investigated what the source of the Artemisin is?

Based on the list of products that caused adverse reactions it seems plausable that the raw materials might have been aldulterated and to make your decision on solid scientific evidence the origine of the raw materials should be investigated.

Artemisia annua ticture is an essential product for prescription in my clinical practice because there are no other plant extracts that express similar phyto-pharmacoloical actions that can be prescribed responsibly by a qualified herbalist.

My research as part of my Masters in innovation & commercialisation specialised in antibacterial plant extracts. Artemisia is of significant importance because it is a key plant product that can provide a therapeutic prescription to assist with a wide variety of bacterial infections.

Artemisinin has been traditionally used for over 5000 years. Please take the application of plants based on cultural heritage into account as part of you decision.

Traditionally, Artemisia extracts are produced using cold water or ethanol. The application of the crude herb might have lead to excessive levels of alkaloids that could lead to the symptoms described in the list of adverse reactions. Please consider the evaluation of different extraction methods before making your decision .

There is a chance that the producers of the products that have cause adverse reactions might not be aware of the phyt-pharmacology of artemisia and therefore choose the wrong type of extraction and manufacturing process. Please consider further investigation.

I am concerned that companies who are not experienced with the pharmacokinetics of plant medicines are causing a change in legislation that is negatively affecting practitioners who prescribe this product responsibly. Therefore I need to ask if you could please consider that herbal medicine practitioners will be exempted from these new regulations considering we are trained professionals who are experienced in the prescription of products that contain Artemisia annua?

Reclassification of codeine – 63rd MCC submission.

Dr Christopher Jones, FANZCA, FFPMANZCA
Specialist Anaesthetist and Specialist Pain Management Physician
CCDHB

Firstly, I fully support option B - that we harmonise with Australia – so that all medicines containing codeine would be classified as prescription medicines.
I am still utterly amazed that we would waste so much time and effort considering any other option when the issues have already been thoroughly examined as part of the now-completed Australian process.

Secondly, I am astounded and appalled that no input seems to have been actively sought from either the Australasian Chapter of Addiction Medicine (AChAM) of the Royal Australasian College of Physicians, or the Faculty of Pain Medicine, Australia and New Zealand College of Anaesthetists.
Codeine is an analgesic agent with the potential for addiction and abuse - why not ask those with expertise in the fields of pain management and addiction treatment for their opinion on the classification of codeine?

Thirdly, the MCC has failed to follow its own guidelines on harmonisation - “in the case of items for harmonisation, the MCC is expected to recommend on whether to harmonise or not, rather than recommend an alternative option”.
In fact, at the same meeting that the nonsensical codeine recommendation was made, the MCC affirmed the principles of harmonisation, (https://www.medsafe.govt.nz/profs/class/harmon.asp). They were consecutive items on the agenda.
The first point of these principles is “[for] both countries there should be… equivalent scheduling for drugs and poisons”. Did the committee members suffer collective amnesia between items 5.3 and 5.4?

Finally – the proposed option C is nonsensical – due to concern about codeine abuse and dependence, the MCC decided to ignore the brilliant Australian decision and make straight codeine more easily available! Many Western countries are suffering from an epidemic of harm due to prescription opioid misuse/ abuse/ dependence – why on earth would we make any opioid in any form more easily accessible?

26th August 2019

The Medicines Classification Committee
Medsafe
PO Box 5013
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Dear Committee Members,

Re: MCC Meeting Number 63 - Codeine and Influenza vaccination administration by Intern Pharmacists

Item 5.3a – Codeine

We are pleased to see the reconsideration of codeine at this meeting, as we feel that it is very possible to retain good access where appropriate for those who benefit from these products, while greatly reducing the potential for misuse or abuse through real-time monitoring. We congratulate the MCC on being able to consider different ways of managing risk and suggest that the real-time monitoring will enable access while maximising safety.

At Green Cross Health, we believe that the implementation of both real-time monitoring and education will resolve the concerns about overuse of non-prescription codeine-containing analgesics. Real-time monitoring reduces the challenge pharmacists experience in needing to make a judgement call on a particular person, often without knowing whether or not they are making purchases elsewhere in excess quantities. Education will maximise the ability of pharmacists to screen for and identify dependence using the real-time monitoring system, and manage it as well as possible if found, to ensure patients get the help they need.

Timeframe

We note the Medsafe document observes that 30 January 2020 is not a practicable time frame given the Medicines Classification Committee consideration in late 2019. It is important for patients, manufacturers and community pharmacy that there is sufficient time to adequately manage patient expectations and stock. We greatly appreciate the comment that Medsafe will work with industry, patient groups and health care professionals to discuss the changes required and determine a suitable timeframe for implementation. As manufacturers will have significant lead times for stock ordering, this is important to consider. We would anticipate that this could easily need a minimum of 12 months. Should Option A be decided on, we agree that four weeks after publication of the minutes would work. However, if real-time monitoring is expected with this, that would take more than four weeks to implement.

We recommend that if Option B (harmonising with Australia) is used, there is a longer time frame than the standard. As we do not know until the very last minute if there has been a valid

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objection, this is effectively no notice. That has important ramifications for patients, pharmacies and manufacturers. We would request a longer period for this change, e.g. three months or more.

The timeframe for Option C is uncertain, which is understandable given the changes in two pieces of legislation. The burden of the legislative changes could be avoided using Option A with real-time monitoring. We believe that this will be at least as effective as Option C in minimising the potential for abuse, but is a more pragmatic approach to the problem, and will allow an earlier change than Option C.

Classification Options

We are comfortable with differing from Australia rather than having harmonisation. There are many cases in which this has occurred, e.g. senna, oseltamivir, oral contraceptives, adapalene, oral cholera and ETEC vaccine, sildenafil, and various vaccines. We agree with the MCC that there is a place for codeine without a prescription and believe that it can be managed safely with real-time monitoring, education of pharmacists and patients, and the already implemented small pack sizes and warnings on the pack.

We see a patient need for the combination products containing codeine. Our members tell us that people purchase them because they find them effective for their pain. Pharmacists often see people with acute pain that needs treatment e.g. dental extraction, headaches, dysmenorrhoea, back pain and so on. If a person finds a medicine particularly effective for them, it is helpful for them to continue to have safe access to it, as our proposal would allow. We acknowledge a small minority of people can have abuse issues. Pharmacists are particularly keen to avoid patient harm and have a long history of doing this with stimulant laxatives, for example. We therefore strongly support using real-time monitoring to retain patient access to medicines that many New Zealanders have found effective for their acute conditions, while minimising the risk of pharmacists inadvertently supplying to a person who is abusing codeine. We also support education (see further information below).

A report by Turning Point in Australia in 2010[1] stated that there was a need to enable pharmacists to respond effectively to the problem of OTC codeine. Pharmacists were considered to be able to "*play an important role in raising general awareness regarding potential OTC codeine dependence and harms.*" However, it was recognised that legislative change and education were required.

The Medsafe information on codeine stated: "*It is not known whether an electronic opioid harm monitoring system will be implemented in New Zealand in the foreseeable future. Therefore it is recommended that the MCC should not consider this as a risk-mitigation strategy when considering the classification of codeine.*"

We note that there has been good progress on real-time monitoring and we understand there are options that could be made ready. We believe others have done work in this space and will be providing more information. Therefore, we recommend Option A with real-time monitoring. Pharmacists want to have reassurance that they are providing codeine-based products appropriately and avoiding codeine misuse in patients. Real-time monitoring enables easy identification of a patient with concerns and an early discussion and referral, if necessary, if use is seen to be higher than that expected or recommended. If abuse or misuse seems likely, the supply would be refused.

Education

Education of pharmacists will help to limit codeine dependence, identify dependence, counsel patients to avoid dependence, and manage suspected cases of dependence in a way that is most likely to see the person take up a referral to a GP or addiction service. There is a risk that patients who are turned away without advice could try to purchase outside of pharmacy, including illicit purchase, and/or go to doctors for codeine. Pharmacists need to be approachable and deal with anyone in whom they suspect addiction in a way that is supportive and with messages that are right for the individual requesting the medication. For our 2017 submission on codeine to the Medicines Classification Committee we had in-depth discussions with a range of pharmacists throughout New Zealand to understand experiences from different communities and their preferences.

One pharmacist reported having persuaded two people with likely dependence to seek help, with opioid substitution therapy started as a consequence. The rural pharmacy he worked in was key to identifying dependence, as patients were more limited in their ability to shop around. His approach also worked well given that one patient was in denial and angry when it was first raised but returned three weeks later for further advice from the pharmacist, which was then followed.

We know that these interactions can sometimes be challenging, particularly if the patient is not well known to the pharmacist or in denial. The other pharmacists spoken to acknowledged that education on this would be helpful, particularly for less experienced pharmacists.

> *"Education would be really great. I'm not always comfortable with these conversations, so that would really help."* Pharmacy Manager, Auckland

> *"It is difficult for younger pharmacists to handle. Education is a great idea. How to deal with it, where to refer people."* Pharmacy Manager, North Island rural pharmacy

The Australian research and report by Turning Point in 2010[1] highlights that the pharmacist interaction was key for some people in highlighting that they had a dependence and getting them to seek treatment for this dependence. It also recommended upskilling the workforce, both pharmacists and doctors, for earlier identification of dependence and how to manage it. The model of Option A with education for pharmacists (and patients) and real-time monitoring is the logical way of following these recommendations.

An education session for pharmacists on OTC codeine was held in early 2017 by the Auckland branch of the Pharmaceutical Society, with Carina Walters speaking. Carina is a pharmacist with extensive experience in addiction services and a PhD candidate examining pharmaceutical opioid dependence. This session was well attended, with positive feedback by pharmacists who attended. The education we propose for pharmacists is outlined below.

Green Cross Health has an NZQA accredited on-line training platform that could be available to all Community Pharmacists (even those outside the Green Cross Health network) and extended teams where appropriate. We intend to use it to provide education to pharmacists that would meet the requirements of the Pharmacy Council's medicines reclassification framework criteria. We would use experts in the area, including Carina Walters (mentioned above). We would expect to include the following information:

- Typical patterns of codeine dependence
- Identifying dependence (e.g. what usage suggests dependence has occurred or may be developing)

- Screening for dependence
- Harms associated with codeine dependence, including clinical effects of overuse of combination products
- Opioid withdrawal and dependence support
- Referral pathways
- Stages of change
- Motivational interviewing/having difficult conversations
- Preventing addiction to codeine

While the training could be expanded to include pain relief generally, we do not recommend this. We want to ensure that the key messages on codeine and identification and management of dependence are not overwhelmed by other information.

Changes in availability through the real-time monitoring needs to be supported through education for health care providers in general practice (e.g. through a BPAC update), available shortly before the change so that general practice can identify and manage codeine dependency as well as possible. GPs and nurses would benefit from being informed of the change in advance through multiple communications (e.g. medical organisations, NZ Doctor, BPAC). Information to emergency departments and after-hours medical clinics would also be useful at the time of the change. Australian researchers identified the need to educate doctors about codeine dependence.[1]

Patient education is also useful. A patient handout to explain the new system, the potential for dependence and what to do if they think they or someone they know may be dependent would help provide useful advice. This could be developed and available on-line for pharmacists to print. Green Cross Health would be happy to support the creation of such a tool, with expert advice.

Monitoring

A nationwide on-line monitoring system could be mandated in the gazette notice. Such a system would use specified photograph ID, e.g. Drivers Licence, Passport or 18+ ID, making purchase under fake names very difficult. The system would likely work in "real-time" – that purchases are immediately available when entering a person's name and identification, from anywhere in the country, and even if it occurred in the last five minutes.

Monitoring that is mandated will mean all supplies to consumers of codeine-based products would need to use the on-line monitoring system and be recorded. This would allow for extensive data reporting.

Having nationwide on-line monitoring of supplies to consumers of codeine-based products would provide pharmacists with an indication of overall usage a patient has had, providing important information that pharmacists are currently missing. The on-line monitoring system would very quickly indicate usage above the recommended daily dose, regular usage within the recommended daily dose (with a potential therapeutic dependence), or escalating usage, which could be addressed as soon as it is identified. Such early detection, and the knowledge of the real-time monitoring, will prevent new addictions. It will indicate anyone with a current dependence very quickly after the system is implemented. Alternatively, it will encourage someone with a dependence to seek help rather than be identified on the system. Some people with an OTC codeine dependence are thought to be unaware that they are

dependent, for example, with daily use where they can think they are medicating pain but it is actually an opioid addiction.[1] These people will be identifiable with this real-time monitoring system and pharmacist education.

The vast majority of people who take codeine-combination analgesics have occasional use without dependency on opioids. Pharmacists have to decide on the appropriateness of supply for these people without the evidence they need. This leads to people with a genuine reason for purchase feeling sometimes that they are being interrogated, and being turned down for supply inappropriately, with considerable potential for offence. It also will lead to people who appear genuine (and many do genuinely have pain conditions)[1] having an unidentified dependency and continuing to be supplied for some time.

The monitoring system can also be a trigger for counselling by the pharmacist for all patients about the fact that dependence can occur and therefore not to take codeine-based products on an ongoing basis.

Australian Evidence

A nationwide real-time monitoring system for codeine-containing OTC medicines was started in Australia by the Pharmacy Guild of Australia in March 2016. The use of MedsASSIST was voluntary for pharmacies, and the pharmacist entered a patient name and identification and then checked the patient history in real-time and saw other OTC codeine purchases. The Guild reported that 72% of pharmacies voluntarily used MedsASSIST at that time.[2] An independent analysis of 49 pharmacies in Western Australia found a 31% reduction in the purchasing of OTC codeine products in the July to December 2016 period versus the matching time period one year earlier.[2] From the 9 million transactions in MedsASSIST, pharmacists identified potential dependence issues (purchasing codeine-containing OTC medicines more than once a month) in 168,000 instances, and counselled the patient. There were around 180,000 cases of no supply. It is a shame that Australia was not able to mandate this system at that time to resolve the issue.

A survey of 585 purchasers of codeine-containing analgesics in pharmacies in Australia found that 93% would support pharmacists supplying codeine without a prescription under strict requirements including real-time monitoring.[2] This is consistent with the Turning Point research in 2010.[1] We would expect a high level of support from consumers in New Zealand also.

Pharmacist Feedback

Before our 2017 submission, our in-depth 20 minute discussions with pharmacists revealed very strong support for the use of real-time monitoring. Quotes included:

> *"The real time thing – it will stop it."* Auckland city pharmacy employee
>
> *"That would be fantastic…. It would give you confidence you are not being spun a load of nonsense. We always suspect is this story truthful?"* Pharmacy owner, Invercargill
>
> *"I'd be very happy to do that in fact I'd like it. I can't see a downside, it would help us."* Suburban pharmacy owner, Auckland
>
> *"That is a good step to be honest."* Employee in a rural pharmacy.
>
> *"That's definitely the way to go."* Rural pharmacy owner.
>
> *"Young pharmacists can be so paranoid it becomes almost a gestapo interrogation."* Pharmacist in a mall pharmacy.

These pharmacists were strongly supportive because it helped their community to have appropriate medication use, and the initiative also supported the pharmacy staff in their work. Some pharmacists volunteered that they thought the problem had reduced in their area over recent years because of the questioning used in the pharmacy and at times when it has not been supplied to a requester. However, these pharmacists still wanted the monitoring system to help ensure they were picking up any dependence early. This is particularly relevant when considering that people with OTC codeine dependence know that when they put in an effort to look respectable (e.g. wearing a suit and tie) and answer the questions right they will be more likely to be sold the product as they appear legitimate.[1]

Some different reasons for people taking excessive OTC codeine identified in Australia included:[1]

- initiating use for pain then transitioning to high dose use after identifying euphoric effects or finding their anxiety or stress decreased
- initiating for pain and having to increase dosing when the pain was no longer responding
- initiating use for recreational purposes and developing a high dose dependence

In the cases listed above the real-time monitoring system would pick up the problem use early.

Need for Codeine

All pharmacists we spoke to in 2017 for our last submission discussed the implications to their legitimate patients who they wanted to have codeine-containing products available for convenient access. Even pharmacists who noted supplying very few packs of codeine-containing analgesics wanted it to remain a treatment option that they and their patients found useful. The cost of attending after-hours services for the treatment of acute pain (e.g. for dental pain at night or in the weekend) if codeine combination products were unavailable would disadvantage people on low incomes, adding to inequities.

Labelling

We are comfortable with the labelling as in Table 6 of the Medsafe document. Having Option A would mean the consumer continued to be able to read these messages, which is particularly helpful when using the tablets or capsules from their medicine cupboard at a later date, as is common with a product for acute pain.

Summary for Codeine

We support a mandatory real-time monitoring system. We support including all codeine containing OTC products in this system.

We also would support education of pharmacists and other health professionals and have already outlined topics that could be included.

6.1 Influenza Vaccination

We strongly support the reclassification of the influenza vaccination, allowing intern pharmacists to administer the influenza vaccination. Increasing numbers of pharmacies are offering vaccines, and in some other countries, particularly Canada and the US, pharmacy students are permitted to vaccinate. It would be helpful to the intern to be able to vaccinate in a learning environment first before going out on their own (with a qualified first aider of course). It would certainly also enable access to the public, because there would be one more staff member able to proactively and knowledgeably discuss vaccines and vaccination with consumers, and another pair of hands to vaccinate, which can be particularly helpful when vaccinating at a workplace setting or having a group getting vaccinations. It would also encourage training to take place early, which will mean future cohorts of qualifying pharmacists will swell the workforce numbers. Many of the currently available locum pharmacists have not been trained in vaccination, limiting access when other pharmacists are away. Having interns trained will, over time, see the entire cohorts of newly qualified pharmacists having the ability to vaccinate, some of whom will move into the locum pool.

6.2 Bilastine

We support the change to increase the pack size for bilastine. This is consistent with other members of this class of medicines with good tolerability and few contraindications and precautions.

Thank you for considering this submission.

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23 August 2019

Dear Jessica,

Thank you for providing this opportunity for the New Zealand Dental Association to provide feedback to the Medicines Classification Committee with regard to the proposed reclassification of medicines containing codeine to one of the following options:

A. to retain the status quo (codeine when in combination with another active ingredient in cough and cold medicines remains classified as a pharmacy-only medicine, codeine when in combination with another active ingredient for analgesia remains classified as a restricted medicine, all other medicines containing codeine remain classified as prescription medicines);

B. to harmonise with Australia (all medicines containing codeine would be classified as prescription medicines); or

C. to reclassify codeine as per the recommendation made at the 59th meeting (medicines containing codeine as the sole active ingredient ≤15 mg per solid dosage unit in packs of not more than 3 days' supply with a maximum daily dose of not more than 90 mg for oral use in adults and children for analgesia be classified as restricted medicines, all other medicines containing codeine would be classified as prescription medicines).

Whilst we acknowledge the literature and issues with respect to abuse, the experience of our members is that codeine is of use in the management of dental pain, particularly in the first forty-eight hours and as a top up when a regime is not giving the desired relief. Codeine is being used routinely in the management of dental pain in combination with other medicines. For that reason, there is merit from a dental perspective in patients being able to access codeine in a combination preparation through a pharmacist, which would be achieved with option A.

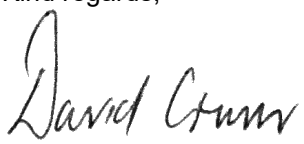
Option B allows control of dose regimen and the way that codeine is used in conjunction with other medicines. It also allows tracking to address concerns relating to adverse reaction and abuse more readily than is currently possible with a restricted classification.

We have concerns about the proposed option C, as it relates specifically to medicines with codeine as the only active ingredient and codeine used in isolation of other medicines is not of assistance in managing dental pain. There is also some concern associated with making it readily available for use in children aged 12 to 18 years, which would be better controlled by a prescription.

While there is merit in the intent of option C, it would necessitate the pharmacist ensuring that the codeine would be used in combination with another medicine/s for example paracetamol or ibuprofen.

I hope that you find these comments of assistance in your determination. Please contact me if you would like further information, or clarification of any of the above points.

Kind regards,



Dr David Crum ONZM
Chief Executive Officer
New Zealand Dental Association

Thank you for the opportunity to comment on the agenda for the 63rd Meeting of the Medicines Classification Committee.

Regulating for safer use of alkyl nitrites

This is a joint submission by the New Zealand Drug Foundation[1] and the New Zealand AIDS Foundation (NZAF)[2] to the Medicines Classification Committee for the October 2019 meeting agenda item around the classification of alkyl nitrites. This submission describes alkyl nitrite use among MSM (Men who have Sex with Men) in New Zealand and provides recommendations for classification based upon the decision by the Australian Therapeutic Goods Administration (TGA).

The final classification of alkyl nitrites by the TGA[3] was positive

The initial proposal emerged from a spike in harm of retinal maculopathy[4] but did not consider the risk of harm from individual alkyl nitrites and suggested an unrealistic blanket scheduling. This approach would have further increased the risk of harm with potential substitution for more toxic and dangerous products and would have pushed this product further into an unregulated black market. Through public consultation[5] and advocacy by the LGBTQI community a more balanced position was reached which was led by evidence and therapeutic considerations. While, the June 2019 TGA decision was an improvement from the currently unregulated market, it does not provide access to fully meet the needs of the community. The decision to have alkyl nitrates as prescription-only medicine creates barriers for people who do not feel comfortable speaking with their doctor, or with doctors who are not unfamiliar with alkyl nitrates. While down-scheduling amyl nitrate to be a pharmacy medicine addresses some of these issues, some people may still struggle to discuss their sexual activity in the open context of a pharmacy.

Alkyl nitrites reduce the risk of harm during receptive anal sex

Also known as poppers, the chemicals have a legitimate beneficial use to enable enjoyable anal sex for MSM (and others). When inhaled, alkyl nitrites cause a non-specific smooth muscle relaxation, including in the sphincter of the anus. This effect facilitates anal penetration and may prevent rectal injury.

International studies show that many MSM experience high levels of distress associated with painful receptive anal intercourse, often referred to as

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[1] https://www.drugfoundation.org.nz/
[2] https://www.nzaf.org.nz/
[3] https://www.tga.gov.au/scheduling-decision-final/final-decisions-matters-referred-march-2019-joint-acms-accs-meeting
[4] Rewbury, R., Hughes, E., Purbrick, R., Prior, S., & Baron, M. (2017) Poppers: legal high with questionable contents? A case series of poppers maculopathy. Br J Ophthalmol, 101: 1530-1534.
[5] https://www.tga.gov.au/alkyl-nitrites-consultation

anodyspareunia. In a US survey, 14% of gay and bisexual respondents reported frequent and severe pain when engaging in receptive anal sex. That study reported that poppers non-use was strongly associated with greater severity of painful receptive intercourse.[6]

A Portuguese study found that moderately or severely distressing anodyspareunia was reported by 17.8% of the participants, presenting as the most frequent sexual problem for gay men.[7]

No therapeutic agents are registered with the indication to enable anal sex for individuals who suffer from painful anal intercourse. Anecdotal evidence suggests some MSM use local numbing creams for anaesthetic effects – their use is not recommended due to loss of sensation of pain without muscle relaxation, that may increase the risk of injury.

Use of alkyl nitrites is common among MSM in New Zealand

Alkyl nitrites currently exist in a grey market. These chemicals are technically classified as medicines but are not available from a doctor or in a pharmaceutical formulation yet, and can be purchased under a guise of not fit for human consumption.

Local research has found that use of poppers is socially acceptable, non-habit forming and used within a sexual setting. A local cohort study this year found 53% of the 836 men surveyed had used poppers once or more in their lifetime and 33% had used them recently (within the past 6 months). Most of this recent use was infrequent with 48% having only used poppers once or twice in the six month period. Only 0.5% of those who had recently used poppers were using them daily.[8]

Previous research found higher rates of recent use with the NZAF 2017 Ending HIV survey finding 37.3% of respondents who were sexually active had used poppers in the past 6 months.[9] Use has been consistent across time with the GOSS 2008 online survey finding 40.1% of respondents having used amyl during sex in the past six months. The face to face part of this research found similar rates of recent amyl use during sex at 41.8%.[10]

Use of these products as a harm minimisation technique was also found. One respondent wrote "I only use poppers with the boyfriend in low doses when I'm a bit tight". There was also evidence that this use was alongside other safe sex

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[6] Damon, W., & Rosser, B. R. (2005). Anodyspareunia in men who have sex with men: prevalence, predictors, consequences and the development of DSM diagnostic criteria. J Sex Marital Ther, 31(2), 129-141.

[7] Peixoto, M. M., & Nobre, P. (2015). Prevalence of sexual problems and associated distress among lesbian and heterosexual women. J Sex Marital Ther, 41(4), 427-439. doi:10.1080/0092623x.2014.918066

[8] Flux NZ 2019 baseline preliminary findings (unpublished)

[9] NZAF Ending HIV 2017 Test Often study (unpublished)

[10] https://www.fmhs.auckland.ac.nz/assets/fmhs/soph/sch/gmsh/docs/BFReport_34LoRes.pdf (p. 70)

practices with the comment "I use poppers during receptive sex (always protected with condoms) and usually only once at the start for the muscle relaxing effect rather than a 'High'."[11]

Increased access to some alkyl nitrites will meet public health goals

Most of the risk from these products comes from the lack of control in the market with no approved product or requirements for accurate labelling. Historically this was not an issue but as more and more alkyl nitrites are banned more harmful substances replace them. This is a common result of prohibition. Further restrictions will not remove harm but lead to more elaborate mechanisms of disguising the product (for example, currently these products can be found in shops masquerading as 'CD cleaner'). A lack of accessibility is a missed opportunity for regulation of a therapeutic product.

Benefit of use needs to be balanced with risk of harm

The introduction of more harmful forms of alkyl nitrites has disrupted the balance of this grey market. This impacts most directly upon the rainbow community with the specific therapeutic role that these products can have as a harm minimisation technique. Balance can be found with a split model of classification as decided in Australia, however wider access beyond pharmacies is needed. Any moves to increase enforcement or reduce availability of currently sold alkyl nitrite products before ensuring a legal viable alternative would be detrimental to the community. This would be a missed opportunity for health promotion and could result in a full shift to the increasingly unpredictable black market.

Reclassify amyl nitrite to increase access

The New Zealand Drug Foundation and NZAF are advocating for:

- Allowing for the regulated sale of amyl nitrite at sex stores, sex on site venues, pharmacies and other health organisations
- Allowing amyl nitrite products approved in Australia to be sold in New Zealand
- Ensuring strict regulations around packaging with child-proof bottles, ingredient lists and guidance on safer use

[11] Flux NZ (2019) responses to question "Would you like to tell us in your own words how you try to keep yourself safe when using or injecting drugs?" (unpublished)

Amyl nitrite is widely researched and has been used in medical formulations in New Zealand previously,[12] and already have exemptions for wider sale.[13] By regulating the least harmful product, as was done in Australia, it ensures a legally viable option and can go a long way to countering risk of harm from the current grey market which is unpredictable and increasingly harmful.

We believe that this can best be achieved with a *general sale* classification of amyl nitrites specifically with location for sale restricted to pharmacies, sex stores, sex on site venues and health organisations. This is preferable to a *pharmacy only* classification, as was agreed upon in Australia, as it matches current access points and is the only model that will reach consumers who are already purchasing unknown products online. If a more restrictive model of *pharmacy only* is required, then allowing exemptions for sales beyond pharmacies is crucial. Sex on site venues and sex stores are both age restricted locations and are well placed to have conversations around safe therapeutic use of poppers, addressing the barrier of having to have conversations on sexual practices in the open context of the pharmacy

The more restrictive *pharmacist only* will greatly reduce access and is likely to have low uptake as it requires disclosure of sexual practice which for some can be difficult, especially those less experienced who would be at greater risk of experiencing harm.

If the cost to enter the market is prohibitive or the cost of a regulated product too high and difficult to obtain then the classification will be futile.

Maintain the *prescription only* classification of other alkyl nitrites

Isobutyl nitrite, butyl nitrite, octyl nitrite and isoamyl nitrite are currently prescription only medications under the Medicines Regulations Act 1984 and following with the Australian decision these should remain.

Further restrict access to most harmful alkyl nitrites

Isopropyl nitrite and n-propyl nitrite are the two chemicals linked to increases in acute harm. They appear to not currently be regulated or restricted in New Zealand. Reducing ability to import or sell these products is necessary to reduce harm, especially if restrictions are provided around the existing sale of prescription only alkyl nitrites. This decision to restrict access was decided in Australia and earlier in France.

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[12] https://www.medsafe.govt.nz/regulatory/DbSearch.asp

[13] 'Amyl nitrite; except when sold to a person who is appropriately authorised under the Health and Safety at Work Act 2015' Schedule one, Part one Medicines Regulations Act 1984

In addition to the points above, we would like to encourage the Committee to review the feedback submitted by the Nitrates Action Group to the TGA consultation, as it gives a detail and nuanced look at the factors involved in reclassification:

https://www.tga.gov.au/sites/default/files/consultation-submission-regulatory-options-alkyl-nitrites-nag.pdf

Thank you for your consideration. Should you require clarification or further discussion on any of the points made, please don't hesitate to contact Samuel Andrews, Harm Reduction Projects Advisor at the New Zealand Drug Foundation at samuel.andrews@drugfoundation.org.nz, or Brooke Hollingshead, Policy Officer at the New Zealand AIDS Foundation at brooke.hollingshead@nzaf.org.nz or on (09) 306 3424.

New Zealand AIDS Foundation
Te Tūāpapa Mate Āraikore o Aotearoa

AT THE HEART OF THE MATTER, NZ DRUG FOUNDATION.
Te Tūāpapa Tarukino o Aotearoa

NZMA
New Zealand Medical Association
Te Hauora mō ngā Iwi Katoa

26 August 2019

Medicines Classification Committee Secretary
By email: committees@moh.govt.nz

Agenda for the 63rd meeting of the Medicines Classification Committee

Dear Sir/Madam

The New Zealand Medical Association (NZMA) wishes to provide comment to the Medicines Classification Committee (MCC) regarding item 6.1 (Influenza Vaccine) on the agenda for the 63rd meeting scheduled for 10 October 2019.

Influenza vaccine is currently a prescription medicine except when administered to a person 13 years of age or over by a registered pharmacist who has completed an approved vaccinator training course. We note the proposed reclassification is to extend administration of influenza vaccine to a registered **intern** pharmacist who has completed an approved vaccinator training course.

We do not believe the submission for reclassification provides a satisfactory rationale for this change and we seek further information on the problem which this proposed reclassification is intended to solve. The claim that the reclassification will help the Ministry of Health deliver increased immunisation rates does not stand up to scrutiny. Under the proposal, intern pharmacists are required to work under the direct supervision of pharmacist vaccinators. The numbers of people who are vaccinated under the reclassification will, therefore, be the same— if the intern doesn't vaccinate, then the supervising pharmacist would. It would be of concern if the main rationale for this reclassification relates to business rather than population health objectives.

Yours sincerely

K. Baddock

Dr Kate Baddock
NZMA Chair

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23 August 2019

Medicines Classification Committee
committees@health.govt.nz

Submission in relation to: 63rd Meeting of the Medicines Classification Committee
Item: 7.2e - Artemisia annua

The New Zealand Pharmacovigilance Centre which operates the Centre for Adverse Reactions Monitoring (CARM), fully supports and endorses Medsafe's Submission to re-classify *Artemisia annua* as a prescription medicine.

The Medsafe report reflects the reports of adverse reactions reported to CARM since the first in 2014 until the data lock point of that report of September 2018. Reports have continued to be received beyond that date. CARM is particularly concerned by the 25 reports of hepatic derangement experienced by users of products that contain *Artemisia annua*, particularly noting that 8 required hospitalisation for liver injury. Diagnostic work up involved multiple blood tests, ultrasound scans and other costlier and invasive procedures including two liver biopsies. The direct harm to affected users and the need to undergo investigations and sometimes hospital admission have resulted in a considerable adverse. impact on affected users' wellbeing, as well as financial implications for them and the health service. The additional observation of QT prolongation in association with the use of *Artemisia annua* products adds a further level of concern.

The evidence that *Artemisia annua* products can cause significant hepatotoxicity and QT prolongation means that they should only be used when the person is likely to benefit and there is clinical supervision to prevent or minimise the risk of serious adverse reactions. It is insufficient to advise potential users to avoid the product if they have liver disorders as liver injury has occurred in users with normal liver function. Early detection of hepatic derangement through monitoring and preventing prolongation of the QT interval by avoiding prescription for those at risk, are standard recommendations to reduce the possibility of serious adverse outcomes. These measures cannot be achieved if access to *Artemisia annua* products is uncontrolled.

The Use of *Artemisia annua* containing products should not be available other than as a prescribed medication.

With Best Wishes

Dr Michael Tatley MBChB, FFCH(SA), FAFPHM, FNZCPHM, BBusSci(Hon)
Director: New Zealand Pharmacovigilance Centre

NZSMI SUBMISSION
TO THE 63rd MEDICINES CLASSIFICATION COMMITTEE MEETING
REGARDING RECLASSIFICATION OF CODEINE

Introduction

NZSMI is New Zealand's premier organisation representing the importers, manufacturers and distributors of over the counter (**OTC**) medicinal products and complementary healthcare (**CHC**) products in New Zealand. Its membership accounts for over 85% of all OTC and complementary healthcare sales in New Zealand. All members submit to abide by a code of practice and it has a fully constituted board comprising the chief executives of the major pharmaceutical companies in New Zealand. It exists to promote the value of self-care in the community by encouraging health literacy and the safe use of clinically proven product. It seeks to work with the Regulator to ensure the New Zealand public has good ready access to well labelled, well marketed and well researched product manufactured to high standards. All manufacturers who distribute OTC codeine in New Zealand are members of NZSMI.

Background

1. The NZSMI position on OTC codeine containing analgesics is:

    1.1 The majority of people who use OTC codeine containing analgesic medicines do so responsibly.

    1.2 Although there has been evidence of adverse events and morbidity reported as a result of dependence on codeine containing analgesics, NZSMI believes that the incidents are low in comparison to the volume of sales and many published reports predate the regulatory action and the intensified monitoring and recording of codeine containing analgesics from 2010 to 2014.

    1.3 There will be potential negative consequences to making OTC codeine containing analgesics prescription only. These include increased costs to government through prescription subsidy and additional pressure on GPs and medical centres, many of whom are currently experiencing long waiting times.

    1.4 Consumers may also be faced with increased out of pocket expenses and the possibility that they may be prescribed higher strength opiates in larger pack sizes as these are currently subsidised by the government. It is noted that this may adversely affect those patients who use codeine products responsibly.

2. NZSMI partially supports retaining the current regulatory classification with special conditions which includes all codeine containing products only being available for sale by a pharmacists and that this sale is recorded in a real time monitoring system.

3. NZSMI therefore does not support the up-scheduling of OTC codeine containing analgesics to prescription only. We strongly oppose the Medsafe recommendation to the MCC that an electronic monitoring system should not be considered as a harm reduction mechanism for the safer use of Pharmacist Only medicines and do support real time monitoring of OTC codeine containing analgesics (and combination products) to allow the sector to better support and enhance a responsible approach on the use of this analgesic class; to reduce the risk of abuse and provide a platform to educate on safe use.

4. In relation to OTC codeine containing cough and cold products that are currently pharmacy only, the NZSMI position is:

   4.1 Cold and flu products typically also contain a decongestant such as phenylephrine in addition to a non-opiate analgesic such as paracetamol. The product indications include pain, however, this is always in the context of, or associated with cold and flu symptoms. These medicines should not be confused with or classed as analgesics. However, given the concern over any codeine containing product we would support an upscheduling of these products to Pharmacist Only.

   4.2 There has been no evidence of abuse or misuse of OTC codeine containing cough and cold medicines currently classified as pharmacy only. It is also interesting to note that when recording processes for codeine containing analgesics were intensified there was no concurrent shift to cough and cold preparations as a source of codeine for abuse.

5. Even given this evidence NZSMI however would support all codeine containing product being restricted to Pharmacist Only sale.

6. There is little evidence that any change to pack sizes is needed. However, NZSMI does believe that a discussion on improved labelling may be warranted. NZSMI notes the recent research regarding children under 18, those with breathing difficulties, and those who have, for example, had tonsillectomies or similar surgery.

7. NZSMI concludes that improved statements could be added to the current list for both analgesics and cough/cold preparations which includes:

   - Do not use for more than 3 days;
   - Codeine is an addictive substance;
   - Do not use if you are breastfeeding except on doctor's advice;
   - This medicine may cause drowsiness;
   - If affected, do not drive a vehicle or operate machinery.

8. NZSMI believes further discussion would be valuable around including statements like:

   - Do not use in children or adolescence under the age of 18;
   - Do not use following tonsillectomy, throat surgery or patients experiencing breathing difficulties.

Pack size reduction

9. There is no evidence that a change to pack size is needed for cold and flu products. Cold and flu medicines are for seasonal use and are used for a condition that is episodic in nature.

10. Limiting the pack size to 3 days may help mitigate against consumers using the product for a prolonged period once purchased for a cold or flu episode and there will be a lesser likelihood of excessive quantities of codeine containing medicine being stored, however, there is no evidence that the use of these medicines has been inappropriate, outside the recommended duration or that stockpiling of these medicines is taking place. It is for this reason that NZSMI would prefer to see increased reporting and monitoring systems established rather than reduction in pack size.

11. It is NZSMI's view that codeine containing cough and cold medicines still have a valuable and safe part to play in a responsibly regulated self-medication industry, particularly if technology

is utilised to better monitor sale and use of these products. The medicine is for a minor ailment or symptoms that can easily be recognised and are unlikely to be confused by the consumer with other more serious diseases or conditions. Treatment can be managed by the consumer without the need for medical intervention beyond that of a pharmacist consultation. The availability of a pharmacist at the point of sale supports the consumer in selecting and using the appropriate medicine.

12. Consumers are able to recognise the symptoms of cold and flu and manage their treatment. Cold and flu, as previously stated, are seasonal and episodic in nature and usually there is a short duration of treatment. Consumers typically consult their doctor when they experience persistent cold and flu symptoms or complications and it is well understood by consumers that cold and flu products are used for temporary relief of symptoms as per the label statements.

13. The use of the medicine is substantially safe for short term treatment and the potential harm from inappropriate use is low. The safety of these combination products is well established and there is no evidence of actual or potential misuse or use by consumers who seek codeine. The presence of additional ingredients, such as decongestants, also mitigates risk in this regard.

14. The use of the medicine at therapeutic dosage levels is unlikely to produce dependency and the medicine is unlikely to be misused, abused or illicitly used. There is no evidence of addiction or dependency occurring from codeine used as per the instructions on the label of OTC codeine containing analgesics.

15. It is the NZSMI's contention that the risk profile of these medicines is well defined and the risk factors can be identified and managed by the consumer with appropriate packaging, labelling and consultation with the pharmacist. There is a low and well characterised incidence of adverse effects, interactions with commonly used substances or food and contra indications. The safety of these combination products is well established and adequate warnings regarding interactions, contraindications and precautions currently appear on the labelling.

16. It is also contended that the use of the medicine at established therapeutic dosage levels is not likely to mask the symptoms or delay diagnosis of a serious condition. It is important to be reminded of what is trying to be achieved here and NZSMI believes that appropriate labelling and packaging with increased pharmacist involvement in sales and recording can manage risks.

17. It is clear from the previous comments that NZSMI's position revolves strongly around changes being made to the reporting system for codeine containing products. We believe this to be a common-sense modern and innovative approach to improved primary healthcare. Later detail will be provided under the section of "Intensified Monitoring".

Codeine containing analgesics

18. NZSMI agrees with the current scheduling of codeine containing medicines as restricted medicines .

19. NZSMI is prepared to further discuss the net overall value of reducing the pack size of codeine containing analgesics to not more than 3 days' supply and also to include warning labels that codeine can cause addiction, however, it is our preferred position that this change on its own will not prove to be useful in reducing the abuse of codeine containing analgesics. NZSMI contends that a more comprehensive real-time reporting of sales and purchaser data is a far more effective and professionally orientated intervention rather than regulated minimum pack sizes.

20. In the event that a reclassification does take place, NZSMI would wish to work with Medsafe on an implementation plan that does not alarm the public, cause stock piling to occur, put medical practitioners at risk or under pressure and allows for an orderly run-out of existing stocks.

Intensified reporting and monitoring of codeine containing medicines

21. It is a known fact that New Zealand does not suffer from the same extent of codeine addiction and OTC abuse evidenced in Australia. The statement on the pack, required by Medsafe since 2011 "Caution:Codeine use can cause addiction" appears to have been effective in reducing the risk and incidence of codeine addiction in New Zealand.

22. If a real-time recording system were to be developed and compulsorily integrated into New Zealand pharmacy, the overall health benefits could be substantial.

23. NZSMI suggests that a two year moratorium (reviewed after one year) on the rescheduling consideration of codeine containing analgesics to allow the development of a nationwide improved mandatory real-time sales and patient data recording system for pharmacy. The benefits of such a system are plainly obvious:

- Only pharmacists who implement the system would be allowed to sell codeine containing analgesics. Only pharmacists who have completed the mandated educational course will be allowed to sell codeine containing product. This education program will include techniques on motivational interviewing as well as handling those patients where drug seeking tendencies have been uncovered.

- Patients would be clearly informed that due to the nature of this medicine their details are required and are held for recording. This highlights the extraordinary or exclusive nature of this particular class of analgesic and lends weight to the need to carefully follow instructions and warnings.

- While not entirely fool proof, the need to produce unique photo ID, e.g. driver's licence, will make life extremely difficult for those wishing to abuse the system as multiple identities would be necessary.

- Codeine use will be simply and accurately monitored and the reporting system will flag very quickly potential abusers.

- Of more importance, the system will also highlight the over-user who is unintentionally 'abusing' codeine containing analgesics and the reporting system provides an easy opening to allow better patient counselling referral and discussion around a potential health issue that is more than a minor ailment.

- Such a reporting system will also improve the relationship between doctors and pharmacists as patients flagged with multiple purchases will activate a response from one or both health professionals.

- In time the system could also be used for other medicines or medicine classes where current reporting systems are seen as inadequate or fragile. This could lead to a greater ease of SWITCH products being accepted for over the counter sales.

- Discussions have already been held with multiple stakeholders around the development of a modernised, digital based system. These include the Pharmacy Guild, Pharmaceutical Society, Green Cross Health and major manufacturers.

- Excellent progress has been made and all parties agree that they will need to contribute funding to make such a system possible. It is our intention that the Ministry of Health would also be involved in this ground breaking initiative as its benefits could well extend far beyond reporting of codeine sales which in the global scheme of primary healthcare is an extremely small cohort.

24. This most important benefit of the proposed real-time monitoring system is that it will be able to accurately identify consumers who visit multiple pharmacies to access products, allowing pharmacists to provide appropriate information and advice to assist consumers who may be having problems with chronic pain, dependence or misuse. There are no comparable software systems in place that record or identify *"doctor shoppers / pharmacy shoppers"* who may have problems with dependence or misuse of prescription opiates.

25. A new intervention process like this will obviously require a well-structured instructional and educational program to work in tandem.

Data collection and analysis

26. Pharmacists will be able to review any other recent codeine containing analgesic purchases to assist in assessing how to best manage the consumer's request. Information entered into the system will be linked in real-time allowing pharmacy shoppers to be identified and referred to their GP or pain clinic as appropriate.

27. This data will also be collected and reported and will provide valuable usage and metadata for better understanding analgesic use in a broad patient base in New Zealand.

28. The intensified reporting and monitoring also opens the door for better patient education by pharmacists on appropriate use of analgesics, not just codeine containing product. NZSMI would like to discuss with Medsafe, the Pharmacy Guild, the Pharmaceutical Society and major pharmacy marketing groups, along with the Self Care Alliance of New Zealand (SCANZ) on how best to develop a consumer education package around appropriate analgesic use.

Education programme

29. In parallel to the development of Pharmacist Only Medicines recording system, NZSMI believes that an intensive education programme needs to be developed that covers medical professionals and prescribers, including specialists, pharmacists, pharmacy staff and the general public.

30. NZSMI has had discussions with major manufacturers who are willing to be involved in the construction of a comprehensive education programme and are prepared to contribute funding.

31. NZSMI also believes that an education Programme endorsed by the Pharmacy Council should be investigated for pharmacists who wish to sell OTC codeine. This programme would cover aspects of appropriate prescribing, appropriate diagnosis and questioning of patients seeking codeine based product, education and advice on the value and risks of codeine containing product, the need and reason behind seeking identification from those wishing to purchase

and the notification that data will be shared or collated on these products. The training would also cover how to manage those patients who have been identified as potential drug seekers.

32. The strategic planning around this education programme has already begun and a timeframe for development and implementation is being worked on. For this reason, NZSMI seeks the moratorium on the existing scheduling of codeine to allow proper development and implementation of the recording system and education programme and suggests that Medsafe could develop reporting milestones that need to be met to maintain this moratorium.

33. This education package and intensified reporting module that is supported sector wide is a major innovation and potential substantial improvement in the delivery of focused primary healthcare.

Other initiatives

34. NZSMI believes that the model created by this initiative of intensified reporting coupled with specialist and public education is capable of being positively scaled for improved benefit at primary healthcare level. NZSMI would then encourage members to look at their current portfolio of products and suggest those which may benefit from better education and better reporting .

35. Members will also be encouraged to look internationally at modern and innovative products that are available in foreign markets that, with appropriate regulation, would sit well in the New Zealand market provided there is intensified monitoring and specialist education. These products are specific, more effective than many old remedies, are in many case technically and pharmacologically advanced, but have not been made available to the New Zealand market because of regulation and less than adequate OTC systems for safe widespread use.

36. NZSMI believes that affordable access to real-time digital innovation is at hand and should be implemented to provide wider access to the safer monitored medicine sales.

Conclusion

37. NZSMI supports an amended Option 1 for the classification of all codeine containing products – the amendment being that:

37.1 the existing classification remains for up to two years to allow time for a nationwide comprehensive, real time reporting system be developed to monitor all sales of codeine containing product;

37.2 that the medical profession, pharmacists and the public are the target of an educational programme, funded by all major stakeholders, on the better use of analgesics including codeine containing analgesics

37.3 that regulations are implemented to require that photo ID must be produced by those wishing to purchase codeine containing product and that they agree to usage data being collated

37.4 that an education program be developed and mandated for any pharmacist wishing to supply codeine and

37.5 that all such sales must be recorded on the real time reporting platform at the time of sale.

38. NZSMI does not believe the upscheduling of codeine containing cough and cold preparations, will improve patient safety or the quality of primary healthcare support such a re-scheduling if it meant the monitoring initiative could be embraced. We also contend that continued education of the medical profession, pharmacists and the public around the responsible and appropriate use of these products.

38.1 NZSMI supports the re-evaluation of this position at the end of the first year of the moratorium on codeine containing products and seeks Medsafe involvement to be party to the monitoring system development.

39. NZSMI believes that this compromised reclassification will lead to a better, safer, more informed primary healthcare sector and that by using modified available technology far better long-term solutions are being developed. The real time monitoring coupled with education, both mandated, will provide a more evidence based approach and could be included as part of the Pharmacy audit process.

August 2019

Kieran O'Donnell
Reece Turner
Directors
NzSupp Limited

30 July 2019

Dear Medicines Classification Committee Secretary

New chemical entities identified by Medsafe – Octodrine

We are writing to provide our comments on a proposed agenda item in the 63rd meeting of the Medicines Classification Committee (MCC). Specifically, we wish to comment on Medsafe's recommendation that Octodrine should be classified as a prescription medicine.

Medsafe prepared an information paper on the classification of Octodrine, however some of the information presented in this paper is misleading given that it refers to substances other than Octodrine, namely DMAA and DMBA. For example, at the beginning of Medsafe's paper, it states that:[1]

> 'There is limited research on the therapeutic benefits and harms associated with the use of octodrine. However, the potential side effects of this stimulant are wide and significant reported adverse events for dimethylbutylamine (DMBA) and 1,3-dimethylamylamine (DMAA) include cardiac, nervous system and psychiatric disorders'.

Put another way, Medsafe explains that there are limited known harms associated with Octodrine, yet then refers to reported adverse effects for separate substances (DMBA and DMAA) to attempt to support its position that there are wide potential side effects of Octodrine. Such a statement is misleading and is likely to misinform readers of Medsafe's information paper.

In addition, Medsafe presents the classification of Octodrine in 'other jurisdictions', including the Ministry for Primary Industries (MPI).[2] Under the MPI jurisdiction, Medsafe discusses a recent systematic review that includes a number of reported adverse effects associated with DMHA. However, this review was not undertaken by the MPI nor appears to be associated with the MPI in any way. By presenting this information under the MPI jurisdiction heading, Medsafe has created the misleading impression that the adverse effects were part of an MPI review, whereas the stated effects in fact represent a list of potential side effects described on a bodybuilding blog.[3]

In our experience, Octodrine based dietary supplements have substantial health benefits. NzSupp has sold

[1] Medsafe, *Classification of octodrine: Information about a New Chemical Entity for the Medicines Classification Committee*, July 2019, p 2.
[2] Medsafe, *Classification of octodrine: Information about a New Chemical Entity for the Medicines Classification Committee*, July 2019, p 3.
[3] The review that Medsafe references is an assessment of literature, websites, drug fora and other online resources, including blogs.

Octodrine products for weight management support and energy support, and we have only received positive feedback from our customers. In particular, our customers have reported that our Octodrine products supported them in maintaining a healthy weight and energy levels. Medsafe has not presented a balanced view of the potential benefits and harms associated with Octodrine and has instead presented the harms associated with different substances (DMAA and DMBA).

In addition, Medsafe has not acknowledged that the list of potential side effects associated with DMHA (as described on the bodybuilding blog) could be due to other ingredients found in DMHA workout products. We note that we have been documenting the sale of DMHA products in New Zealand since 2014, and are aware that many producers of DMHA workout products combine DMHA with high doses of caffeine and/or other stimulants. A high dose of caffeine can be responsible for all of the potential side effects described on the workout blog. Comparatively, NzSupp has sold Octodrine as a simple product by itself for the past four years and has not found any of these side effects.

In addition to presenting misleading information, some of the information contained in Medsafe's paper is incorrect. For example, Medsafe state that:[4]

1. 'Some products claim that octodrine comes naturally from plants and have been labelled as Kigelia Africana extract, but there is no clear evidence that octodrine can be found in these plants'.
2. 'Products containing octodrine does [sic] not meet any of the requirements to be defined as a dietary supplement'.
3. It 'has received advice that octodrine is a medicine as it is only added to products for a therapeutic effect, despite any absence of therapeutic purpose claims for the finished product. There does not seem to be any other reason for octodrine to be added to the product other than for a therapeutic effect.'
4. 'it appears that most of the octodrine being manufactured for supply is synthetic'.

We explain that each of the above statements are incorrect in the remainder of this letter, as well as provide a suggested approach for the classification of Octodrine.

1. Octodrine can be found in plants

Although Medsafe states that there is 'no clear evidence that octodrine can be found in these plants', the article that Medsafe references at page three of its information paper explains that:[5]

> 'Structurally, there are two forms of DMHA [octodrine]: the naturally occurring 2-amino-5methylpetane and the synthetically derived 2-amino-6-methylheptane. The natural version can be found in extracts of Juglans Regia (Walnut Bark), Aconitum Kusnezoffii's and Kigelia Africana…'

[4] Medsafe, *Classification of octodrine: Information about a New Chemical Entity for the Medicines Classification Committee*, July 2019, pp 2-3.
[5] Catalani V, Prilutskaya M, Al-Imam A, et al. Octodrine: New Questions and Challenges in Sport Supplements. *Brain Sci.* 2018;8(2):34. Published 2018 Feb 20.

This article provides clear evidence that Octodrine/DMHA is found in a number of plants, including walnut bark and Kigelia Africana fruit.

However, the article referenced by Medsafe typically contains information sourced from blogs as opposed to scientific studies. As such, some of the information presented in this article is incomplete or incorrect. For example, the article does not explain that there is only one form of Octodrine, which is 2-amino-**6**-methylheptane. The term 'DMHA' is used by the supplement industry, and captures two products, both of which are found in nature.

The first form of DMHA is 2-amino-**5**-methylheptane and is found in Juglans Regia (English walnut tree).[6] This version is the strongest form of DMHA and cannot correctly be called "Octodrine" because it has a different chemical formula from Octodrine.

The second form of DMHA is Octodrine (2-amino-**6**-methylheptane) and is found in a number of plants, most notably the Kigelia Africana fruit.[7] In other words, not all DMHA can be called Octodrine, with Octodrine being one of the two forms of DMHA.

2. Octodrine meets dietary supplement requirements

Medsafe states that Octodrine does not meet the definition of a dietary supplement, however it does not provide any support for this statement. We understand that a dietary supplement is defined in the *Dietary Supplements Regulations 1985* as:

> '…something to which subclauses (2) to (6) apply.
>
> (2) It is an amino acid, edible substance, herb, mineral, synthetic nutrient, or vitamin.
>
> (3) It is sold by itself or in a mixture.
>
> (4) It is sold in a controlled dosage form as a liquid, powder, or tablet (which might be described on the label as a cachet, capsule, lozenge, or pastille instead of as a tablet).
>
> (5) It is intended to be ingested orally.
>
> (6) It is intended to supplement the amount of the amino acid, edible substance, herb, mineral, synthetic nutrient, or vitamin normally derived from food.'

We explain below that Octodrine meets all of the subclauses of clause 2A of the *Dietary Supplements Regulations 1985*, and consequently can be classified as a dietary supplement.

(2) It is an amino acid, edible substance, herb, mineral, synthetic nutrient, or vitamin

[6] Shinwari, Mahera & Ara, Ismet. (2015). Evaluation of Antimicrobial Properties of Two Different Extracts of Juglans regia Tree Bark and Search for Their Compounds Using Gas Chromatography-Mass Spectrum. Available here: https://mma.prnewswire.com/media/873401/dmha_HiTech.pdf?p=original.

[7] Arkhipov, Alexander & Shalom, Joseph & Matthews, Ben & Cock, Ian. (2014). Metabolomic Profiling of Kigelia africana Extracts with Anti-Cancer Activity by High Resolution Tandem Mass Spectroscopy. Pharmacognosy Communications. Available here: https://core.ac.uk/download/pdf/143854406.pdf.

Octodrine is classified as a synthetic nutrient. Specifically, Octodrine is a phytochemical (ie, a non-nutritive chemical found in plants) – a study by Griffith University, Australia identified Octodrine as one of the phytochemicals of Kigelia Africana fruit.[8] Other examples of phytochemicals include caffeine, theobromine, limonene, beta-Sitosterol, resveratrol, and plant antioxidants. Phytochemicals are classified as non-essential nutrients and are captured by sub-clause 2 of clause 2A of the *Dietary Supplements Regulations 1985*.[9]

(3) It is sold by itself or in a mixture

Octodrine for use in weight management support or energy support products is typically sold in capsules by itself and in a mixture.

(4) It is sold in a controlled dosage form as a liquid, powder, or tablet (which might be described on the label as a cachet, capsule, lozenge, or pastille instead of as a tablet)

Octodrine for use in weight management support or energy support products is typically sold in a controlled dose in the form of a powder or capsule.

(5) It is intended to be ingested orally

Octodrine products are only to be ingested orally.

(6) It is intended to supplement the amount of the amino acid, edible substance, herb, mineral, synthetic nutrient, or vitamin normally derived from food

As stated earlier, DMHA is found in multiple natural sources, namely the English walnut tree (Juglans Regia) and the Kigelia Africana fruit. Moreover, Octodrine is listed on the independent natural database for food, herbs and dietary supplements.[10]

The English walnut tree is grown in New Zealand, with the trees sold for their edible nuts.[11] In addition, some pharmacies sell Juglans Regia extract.[12] Comparatively, Kigelia Africana, is grown in South East Asia and Australia. The plant has been traditionally used for thousands of years and is available throughout the world.[13] The fruit is dried to be consumed and the seeds are also considered edible when roasted.[14]

3. Therapeutic effect of Octodrine

Medsafe states that it 'has received advice that octodrine is a medicine as it is only added to products for a therapeutic effect', suggesting that products with a 'therapeutic effect' are classified as medicines.[15] However, this implied approach of classifying products with a 'therapeutic effect' as medicines is not in

[8] Arkhipov, A., P, J., Matthews, B., & Cock, I. (2014). Metabolomic Profiling of Kigelia africana Extracts with Anti-Cancer Activity by High Resolution Tandem Mass Spectroscopy. Pharmacognosy Communications, 4(4), 19.
[9] See for example: http://www.phytochemicals.info/.
[10] Natural Medicines website, https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements.aspx?letter=O.
[11] See for example: https://www.southernwoods.co.nz/shop/juglans-regia-rex/.
[12] See for example: https://www.pharmacydirect.co.nz/Bach-Original-Flower-Remedies-Walnut-Drops-10ml.html.
[13] See for example: https://ilovekigelia.com/about; https://www.natureshop.com.au/products/kigelia-extract; and https://www.amazon.com/Kigelia-Alcohol-FREE-Africana-Glycerite-Supplement/dp/B01A3PD96S?th=1.
[14] See for example: https://fairdinkumseeds.com/products-page/ethnobotanical-or-medicinal-plants/sausage-tree-kigelia-africana-pinnata-seeds/.
[15] Medsafe, *Classification of octodrine: Information about a New Chemical Entity for the Medicines Classification Committee*, July 2019, p 2.

line with New Zealand legislation.

The *Medicines Act 1981* (the Act) defines a medicine as a product for which a therapeutic purpose is intended, with the term therapeutic purpose also defined in the Act. However, the term 'therapeutic effect' as used by Medsafe is not used in the Act nor does it indicate that all substances with such an effect are classified as medicines.

By contrast, the Act requires that medicines have a therapeutic purpose – ie, products administered to prevent, diagnose, monitor, alleviate, treat, or cure a disease, ailment, defect, or injury. As such, Medsafe's approach to classify Octodrine by considering the effectiveness of the product, as opposed to whether it has a therapeutic purpose is not in line with the definition of a medicine as set out in the Act.

Moreover, dietary supplements typically contain therapeutically active ingredients and, as such, the inclusion of a therapeutically active ingredient cannot be used to classify a product as a medicine. Indeed, Food Standards Australia New Zealand (FSANZ) define 'active ingredients' as:[16]

> *[t]he therapeutically active ingredients found in dietary supplements, including nutrient substances as well as ingredients that contribute caffeine and cholesterol.*

If all dietary supplements containing therapeutically active ingredients were to be classified as medicines, then only those products found to be ineffective could be classified as dietary supplements and all effective dietary supplements would meet Medsafe's erroneous definition of a medicine.

For example, Caffeine and Theacrine (derived from tea) are commonly included in supplements and have known stimulant effects. Under Medsafe's proposed classification of a medicine, both of these products would be found to have 'therapeutic effects' and would therefore be classified as medicines. The same would be true for all dietary supplements that effectively provide a wellness effect.

4. Octodrine being manufactured for supply is synthetic

Medsafe noted that 'it appears that most of the octodrine being manufactured for supply is synthetic'.[17] However, New Zealand regulations do not prohibit synthetic substances from being classified as dietary supplements – moreover, clause 2A of the *Dietary Supplements Regulations 1985* states that dietary supplements includes synthetic nutrients (DMHA is a synthetic nutrient). Indeed, many dietary supplements are synthetic and made to the same strict requirements as Octodrine. For example, Vitamin C and multivitamins are typically made from synthetic ingredients.

Suggested classification of Octodrine

As explained earlier in this letter, there are two forms of DMHA (which include Octodrine), with both forms of DMHA meeting the definition of a dietary supplement under the *Dietary Supplements Regulations.* Therefore, we suggest that both forms of DMHA should be classified as dietary

[16] FSANZ website, http://www.foodstandards.gov.au/science/monitoringnutrients/ausnut/Pages/glossary.aspx.
[17] Medsafe, *Classification of octodrine: Information about a New Chemical Entity for the Medicines Classification Committee*, July 2019, p 2.

supplements.

Furthermore, we note that Medsafe's mission is to 'apply processes that are consistent and transparent'.[18] As such, we request that Medsafe and the MMC apply an approach to classify Octodrine that is both transparent and consistent with the assessment of other dietary supplements. That is, we request that Octodrine be classified using an approach that is consistent with the classification of other dietary supplements – ie, if the same approach was applied all other dietary supplements, it would still classify these substances as dietary supplements as opposed to medicines.

If you require any further information, please either email us at nzsupp@hushmail.com or call 027 600 0324.

Yours sincerely

Kieran O'Donnell
Reece Turner
Directors
NzSupp Limited

[18] Medsafe website, https://www.medsafe.govt.nz/other/about.asp#do.

PHARMACY GUILD OF NEW ZEALAND

26 August 2019

Medicines Classification Committee Secretary
Medsafe
Wellington

Sent via email to: committees@moh.govt.nz

Dear Committee Members

RE: Agenda for the 63rd meeting of the Medicines Classification Committee

Thank you for the opportunity to provide feedback on the agenda for the 63rd meeting of the Medicines Classification Committee (MCC), to be held on 10 October 2019.

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.

Our feedback covers three agenda items. These are:

- Agenda item: 5.3a Reclassification of codeine
- Agenda item: 6.1 Influenza vaccine – proposed change to the Prescription classification statement (Pharmaceutical Society of New Zealand)
- Agenda item: 6.2 Bilastine - proposed change to the Pharmacy Only classification statement (Menarini New Zealand Pty Ltd)

Each of these agenda items are discussed below.

Agenda item: 5.3a Reclassification of codeine

The Guild **supports** the classification of codeine to remain as **status quo (option A)** and to not be harmonised with Australia. We are opposed to a reclassification of codeine containing medicines that would lead to significant access and equity issues for patients.

Community pharmacies in New Zealand play a significant role in ensuring patients have access to health care in an efficient and timely manner. The harmonisation of the classification of codeine to prescription-only will significantly restrict access for people who genuinely need these medicines for legitimate purposes. The harmonisation of codeine will also lead to inequities for people who access these medicines through community pharmacies who either cannot afford to see their doctor or are not able to get an appointment to see their doctor in a timely manner.

The cost of codeine containing medicines through pharmacy are generally more affordable than having to go to see a doctor and to pay for a prescription to be dispensed for an equivalent treatment. Making codeine only available on a prescription will create significant financial and access barriers for patients needing treatment for acute pain and discomfort, and for symptomatic relief of the cold and flu.

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The primary goal of the Pharmacy Action Plan is for people to have equitable access to medicines and health care services. One of the focus areas is to develop a minor ailments and referral scheme in New Zealand to allow pharmacists to use their clinical training to triage, then treat or refer patients. This will provide timely access and reduce the burden on general practice and secondary care services.

Reclassifying codeine containing medicines will go against the aspirations of the Pharmacy Action Plan and the focus of developing a minor ailments and referral scheme. Pharmacists use their clinical training to not only provide the appropriate treatments to patients but to also refer them to their doctor. Reclassifying codeine will remove a significant opportunity for pharmacists to assist as part of a wider health care team. If the opportunity is removed, this will lead to patients who cannot afford to see the doctor to either delay accessing treatment or to not seek it at all. This will also lead to an increase in unnecessary presentations at general practice, reducing the capacity for doctors to focus on patients with more urgent needs.

Due to a current doctor shortage, the general practice sector is under considerable workforce pressures, with estimations that half of the current workforce are planning to retire within the next ten years. We regularly hear of an ever-growing number of medical centres having to close their books to new patients, with this being particularly more prevalence in rural areas. In rural areas, access to timely health care is already limited, with pharmacy playing a pivotal role to help fill the gaps unable to be met by general practice. Reclassifying codeine to prescription-only will only further the inequities in these areas to accessing health care.

We are not convinced that changing the classification of codeine to be managed by a doctor will solve the problem of codeine misuse that Medsafe is trying to address. We feel this will only shift the problem, rather than help to resolve codeine misuse. Currently, a significant majority of codeine use is already on a prescription, often in higher strengths and larger quantities that what would be purchased in a pharmacy. From a monitoring perspective, doctors do not have any more ready access to real-time monitoring systems than what is available at a pharmacy.

Instead, we would like Medsafe to empower both professions to work together to monitor and refer patients as necessary to ensure that patients get the appropriate treatment and are not disadvantaged in where they access that treatment from. Pharmacists have a responsibility under their Code of Ethics to prevent the unnecessary and excessive supply of codeine containing medicines. This is further guided by the joint Pharmacy Council and Pharmaceutical Society statement on the sale of codeine containing analgesics that has been discussed at previous MCC meetings.

The current issue of managing the misuse of medicines comes largely from the inability of health professionals to be able to track and monitor the usage of patient medication outside of their own databases. The monitoring of the misuse of medicines can only truly occur when health professionals can see a true representation of a patient's complete medication record.

We recommend that Medsafe should allow for the supply of codeine containing medicines to continue on the proviso that a real-time monitoring system is used as part of the sale and supply of these medicines. We believe that by requiring the usage of a real-time

monitoring system, this will allow for early detection of codeine misuse, helping to address the issue earlier. This will also ensure that timely patient access to these medicines will remain and that patients will not be disadvantaged by where they access these medicines from. By being able to monitor the usage of these medicines appropriately, this will allow for the opportunity to refer the affected patients appropriately, therefore leading to better patient outcomes.

In our previous submission to the 59th meeting, we commented that we were in the process of implementing an appropriate real-time monitoring system. However, due to the significant investment required by the sector, the final decision was dependent on whether codeine containing medicines would still be available to justify the significant investment required. In the time since the 59th meeting, there has been significant technological enablement across New Zealand, where there are now several appropriate shared-care platforms and other real-time monitoring systems that have become available for health professionals to access. These systems allow for patient dispensing records to not only be accessible to other pharmacies but also to communicate with general practice and hospitals as part of a wider health ecosystem.

As the systems are either currently available or soon to be available, this will allow for a relatively quick implementation of a real-time monitoring system, compared to previously, where we were looking at implementing an entirely new system into community pharmacy.

Electronic opioid harm monitoring system

Page 13 of the 'Classification of codeine report', refers to no known availability of electronic opioid harm monitoring systems in New Zealand. Therefore, the report recommended that the MCC should not consider this as a risk-mitigation strategy when considering the classification of codeine.

However, as discussed, we are aware of a number of real-time monitoring systems currently in use or under development in New Zealand. We therefore request appropriate consideration be given to these systems as a suitable risk-mitigation strategy when considering the classification of codeine.

Below we outline the real-time monitoring systems that are currently available or are soon to be available in New Zealand.

1. <u>Conporto EDM</u>

Conporto Health has an Event Detection and Mitigation (EDM) service which helps health professionals minimise the risk of treatment harm to patients.

The Conporto platform works across databases held by hospitals, general practices and pharmacies, searching the patient's medication history in all locations at once, identifying if a risk of harm is likely. The Conporto EDM service allows search parameters to be set in the system and can be customised to detect any medication related incident.

By way of example, Conporto and ACC are currently running a trial where parameters have been setup up to help with harm minimisation of sodium valproate. When a pharmacy dispenses sodium valproate, Conporto EDM searches the patient history within the databases that Conporto can access as part of their ecosystem, for any dispensings

of contraception. If the system cannot detect a dispensing for contraception it will create a notification to alert the pharmacist. This notification will alert the pharmacist to have a consultation with the patient to provide information about the importance of contraception while taking sodium valproate and to provide the patient with the sodium valproate information booklet produced by the Ministry of Health, ACC and HQSC.

We have had discussions with Conporto about setting parameters for the detection of patient codeine usage within a specified period of time. This would set parameters to detect both the dispensing and prescribing of codeine containing medicines. The service will create a notification if it detects repeat codeine dispensing or prescribing within a specified period of time, enabling the health professional to manage any codeine misuse.

Conporto EDM is a simple software installation, that only takes 10 minutes to install and requires a web browser and internet connection, which all pharmacies have. Conporto have informed us that Conporto EDM is already available in 60% of community pharmacies in New Zealand.

From our understanding, the implementation time is minimal as setting up the appropriate parameters is virtually instantaneous and once the parameters are determined, the service can go live immediately. As this software has already been developed and is ready to be used, this will allow for a relatively quick implementation period to get the service up and running in the remaining pharmacies in New Zealand and for the service to become live.

2. Shared-care platforms

The majority of community pharmacies already have access to shared care platforms through their DHB. Currently, 12 out of 20 DHBs have shared care platforms:

- TestSafe – Northland, Auckland, Waitemata, Counties Manukau DHBs
- Conporto – Capital Coast, Hutt Valley, Wairarapa DHBs
- HealthOne – All of the South Island

By having access to shared-care platforms, community pharmacists can access patient medicine related records from general practices, hospitals and community pharmacies. These include patient prescription dispensing histories, allowing all pharmacies within the coverage of the shared-care platform to see the dispensing histories of all patients.

Currently, pharmacist-only medicine sales are mostly recorded in the over-the-counter component of the pharmacy software, therefore these sales are not automatically uploaded to the shared-care platform.

However, if these sales are processed against the name of the patient through the pharmacy dispensing software it will ensure these medicines are recorded on the shared-care platforms. The recording of these sales on the shared-care platform will enable the tracking of a patient's usage of codeine containing medicines.

Even though there is not a system that is available nationwide, the advice we have received is that it is relatively straight forward to enable the various shared care systems to speak to each other. Currently, the development of a shared-care platform is focussed around ensuring optimal benefit to the local providers.

This is aligned with our understanding that drug seekers generally visit pharmacies within their DHB catchment, and it is unlikely the majority of these individuals would go outside of their locality.

3. Toniq

The Toniq pharmacy management system is used by over 900 pharmacies throughout New Zealand, with the remaining pharmacies using the RxOne pharmacy management system.

Currently, pharmacy management systems are unable to communicate between pharmacies. However, Toniq are developing a unified medication management platform which will allow for all Toniq users to access a unified patient medication history. Toniq are currently in discussion with the Ministry of Health and plan to have their unified medication management platform live by the end of this year.

In the same way as described with a shared-care platform, all Toniq users will be able to check the patient's unified medication history at the time of supplying over-the-counter codeine containing medicines and mitigate patient misuse of these medicines.

4. New Zealand Electronic Prescription Service (NZePS)

The NZePS is an electronic prescription broker service that is available in all pharmacies throughout New Zealand. It allows secured exchange of electronic prescription information for prescribing and dispensing systems. Currently, at the time of dispensing, pharmacies can receive prescriber comments related to a prescription, and prescribers can request notification when a patient's medication has not been dispensed.

It is our understanding that all dispensed prescriptions, whether they are electronic prescriptions or not, go through the NZePS broker. Therefore, all prescriptions that are dispensed by community pharmacies are recorded through the broker, in effect providing the basis for a real-time monitoring system. Currently, patient medicines information can be accessed through one of the shared-care platforms by the health professional completing the required security questions each time access is required.

Sharing of patient information

Page 19 of the 'Classification of codeine report', states:
Information on previous purchases of codeine containing medicines may give a pharmacist more information about the frequency of purchases from other pharmacies to help identify potential misuse. However, the sharing of information obtained by the pharmacy following an over-the-counter sale is limited by the Health Information Privacy Code 1994. Rule 11 of the Health Information Privacy Code prohibits the disclosure of health information except under very specific circumstances. These may not allow for monitoring or post-market surveillance activities of routine sales of codeine containing medicines.

For clarity, Rule 11 allows the disclosure of patient information where there is a purpose. To ensure pharmacies are meeting their obligations under the code, pharmacies need to display the appropriate warning notice in at least one appropriate and easily visible place within the pharmacy.

In 2016, the Pharmacy Defence Association (PDA) together with the Head of the Drug Squad at the Police, the Police legal advisor and the Privacy Commissioner, drafted a warning notice (see Appendix 1) for community pharmacies to use for this purpose. This warning notice enables the sharing of patient information to help in the monitoring of the inappropriate use of medicines that may be abused or used for illegal purposes.

The warning notice covers the pharmacy's obligations under Rule 3 which includes what information may be collected, why it is being collected and who it may be shared with, which is compliant with what patients need to know under the Privacy Code.

This is the guidance provided by PDA to pharmacists on 13 March 2016:
PDA has been working closely with the NZ Police to formulate a sign you can display in your pharmacy to notify people purchasing codeine and other medicines of potential abuse, that their details can be passed on legally to the Police or other pharmacies.

For you to be able to use this information, you must print the attached page titled "Preventing Drug Abuse" and display it in at least one appropriate and easily visible place within your pharmacy (e.g. on the shop counter or next to where the pharmacist only medicines are kept). By doing so you are meeting any confidentiality requirements under the Privacy Act 1993.

If you have suspicions about a certain person abusing certain medicines you may send this information to the local police station or local pharmacies where this person could also be presenting.

To further assist pharmacies in meeting the appropriate disclosures under the privacy code, we have recently created a Health Information Privacy Policy for community pharmacies (see Appendix 2). Community pharmacies are obligated under the Code of Rights to display this policy to ensure that patients are informed about how pharmacies use their health information.

Agenda item: 6.1 Influenza vaccine – proposed change to the Prescription classification statement (Pharmaceutical Society of New Zealand)

We **support** the proposed amendment to the 'prescription except when' classification of the influenza vaccine to include registered intern pharmacists who have successfully completed a vaccinator training course approved by the Ministry of Health and who are complying with the immunisation standards of the Ministry of Health.

This classification change will enable pharmacists to further assist the Ministry of Health to improve immunisation rates throughout the country. Pharmacists are often regarded as the most accessible health professional, so increasing the number of pharmacists who can provide vaccinations will further increase patient access to the influenza vaccine.

As seen both in New Zealand and overseas, vaccinations are becoming part of the core function of a pharmacist. Allowing intern pharmacists to provide the influenza vaccine will help compliment the training they receive throughout the intern training programme and will allow them to be qualified vaccinators by the time they become a registered pharmacist.

This classification change will also help reduce barriers to accessing the vaccinator training programme by enabling the training to become part of the intern training programme. This is particularly beneficial for pharmacists located in areas where the vaccinator training programmes are not provided.

We also see benefits in the classification change for smaller pharmacies that may be limited in their ability to vaccinate patients due to staff availability. Enabling intern pharmacists to provide the influenza vaccine will improve the availability of vaccinating pharmacists, which will have significant benefits to ensuring the continuity of the pharmacy's vaccination service throughout their opening hours, improving patient access to the influenza vaccine.

Agenda item: 6.2 Bilastine - proposed change to the Pharmacy Only classification statement (Menarini New Zealand Pty Ltd)

We **support** the removal of the maximum pack size from bilastine 20mg tablets. This will align with other non-sedating antihistamine tablets available in New Zealand.

Thank you for your consideration of our response. If you have any questions about our feedback, please contact our Professional Services Pharmacist, Alastair Shum, at alastair@pgnz.org.nz or on 04 802 8209.

Yours sincerely,

Nicole Rickman
General Manager – Membership and Professional Services

Appendix 1:

Preventing Drug Abuse

This pharmacy is working with New Zealand Police to monitor inappropriate use of medicines that may be abused or used for illegal purposes, including those that contain codeine.

We may request identification and record information for the sale of some medicines. This information may be passed onto Police as part of our work to prevent the abuse and illegal use of medicines.

With this in mind and because some medicines are not always suitable for some people, we reserve the right to decline your request to purchase a medicine or dispense a prescription.

We are also part of a network of pharmacies that shares information about attempts to have false prescriptions filled or to bulk-buy medicine for illegal purposes.

Customers purchasing medicines for legitimate use can be reassured that their information will be treated confidentially, in accordance with the Privacy Act.

pharmacydefence ASSOCIATION

PHARMACY GUILD OF NEW ZEALAND

PHARMACEUTICAL SOCIETY of New Zealand Incorporated

New Zealand POLICE Nga Pirihimana O Aotearoa

Appendix 2:

PHARMACY GUILD
OF NEW ZEALAND

Health information privacy policy

The Health Information Privacy Code 1994 requires us to tell you about how we collect, store, use and share your personal information. Your privacy is very important to us. The following outlines our health information privacy policy.

Collection and use of your personal information

- We will collect your personal information by lawful and fair means, ensure it is accurate and current. Where appropriate, this will be with your knowledge or consent.
- We will collect and use your personal information solely with the objective of fulfilling those purposes associated with dispensing and managing your medicines and for other compatible purposes associated with your care and treatment; unless we otherwise obtain your consent or as required by law.

Storage of your personal information

- We will protect your personal information by reasonable security safeguards against loss or theft, as well as unauthorized access, disclosure, copying, use or modification. When it is no longer required, the information will be disposed of in a manner that preserves your privacy.
- We will only retain personal information as long as necessary for the fulfilment of those purposes for which the information was collected, subject to the Health (Retention of Health Information) Regulations 1996.

Access to and correction of your personal information

- You can ask us for a copy of your personal information at any time. Under the Privacy Act 1993, you are entitled to request access or correction to the personal information held by us.
- Where applicable, we may charge a fee for responding to a request for access to and/or disclosure of personal information.

Sharing of your personal information

- We will share your personal information with the District Health Board and Ministry of Health to obtain subsidised funding for your medicines and health care services, or for audit purposes, or to other providers if you have a claim related to your treatment.
- We will only use and share personal information where necessary to carry out the functions for which we collected it, or if required by law.
- We will ensure we comply with the Pharmacy Council Code of Ethics, if there is any disclosure to:
  - your nominated next of kin and/or health care providers (if applicable to the services being provided to you)
  - emergency services (if applicable to the services being provided to you).
- In the event of this pharmacy substantially selling all of its assets or being acquired by a third party, personal information held about its customers will be one of those transferred assets.
- Records on your prescriptions dispensed at this pharmacy are available electronically to authorised health care providers involved in your care via a secure database known as NZePS / HealthOne / Testsafe.

PHYTOmed™
medicinal herbs ltd.

19 August 2019

Secretary
Medicines Classification Committee
Ministry of Health
133 Molesworth Street
Thorndon
Wellington 6011

FEEDBACK ON PROPOSED RE-SCHEDULING OF ARTEMISIA ANNUA TO BE PRESCRIPTION ONLY

This submission is being made on behalf of Phytomed as we are aware of a submission made by Medsafe to the Medicines Classification Committee in June, to classify Artemisia annua and its extracts, as a prescription medicine.

We recommend that the Medicines Classification Committee:

1. Does not classify Artemisia annua and its extracts as a prescription medicine.

2. Recommends to Medsafe and the Minister of Health that New Zealand's regulatory regime requires all natural-health products making therapeutic claims to be manufactured in a GMP certified facility.

3. Recommends to Medsafe and the Minister of Health that New Zealand's regulatory regime moves to a complementary medicines-based model and away from a dietary supplement model.

4. Recommends to Medsafe and the Minister of Health that New Zealand's regulatory regime requires all herbs and raw materials included in complementary medicines to be subject to a rigorous testing regime.

5. Recommends to Health Workforce NZ that New Zealand regulates the professional practice of western Herbal Medicine, as applied for by the New Zealand Association of Medical Herbalists (NZAMH), under the Health Practitioners Assurance Act.

We do not believe that the root cause of the 14 New Zealand reported cases of hepatotoxicity associated with Artemisia annua, are due to the safety of the herb. The most likely cause, given international evidence, is in the quality and/or contamination of the herb and in the manufacturing processes. Classifying it a prescription only medicine does not address the root cause. Also, making it a prescription only medicine would take it out of the reach of the many natural health practitioners and others, who currently rely on it in their daily lives.

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PHYTOmed™
medicinal herbs ltd.

About Phytomed

Phytomed Medicinal Herbs Ltd (Phytomed) is a GMP-licensed company that since 1998, has manufactured herbal medicines, including an Artemisia annua hydroethanolic liquid extract sold to suitably qualified practitioners in New Zealand. The company has a comprehensive Pharmacovigilance system in place and employs staff with knowledge in the area of Pharmacovigilance in relation to Herbal Medicines, as well as in the procurement and testing, and quality assurance assessment of more than 250 different types of herbal raw materials.

Phytomed's Technical Director, Phil Rasmussen, was the NZ Chair of the Interim Expert Committee on Complementary and Alternative Medicines established by the Australian and New Zealand governments between 2006-2008, and from 2016 to 2017 was Chair of the Interim Technical Expert Committee, Natural Health Products (Permitted Substances Subcommittee), appointed by the New Zealand Ministry of Health.

About Artemisia annua

Artemisia annua is currently an unscheduled substance in New Zealand, and products containing *Artemisia annua* extract are sold in the form of:

1. Dietary supplements, such as Arthrem and Go Arthi-Remedy, promoted for maintaining and supporting joint health and mobility. They can be purchased from pharmacies and online.

2. Traditional Chinese Medicine (TCM) practitioner prescribed formulations, taken by patients following consultations with TCM practitioners.

3. Western Medical Herbalist practitioner prescribed formulations, taken by patients following consultations with naturopaths or medical herbalists who have generally been trained in NZ.

4. Imported mainly Traditional Chinese Medicine-based proprietary products, from Asian countries and purchased OTC predominantly by Asian ethnic communities.

We are aware of two small clinical trials involving Artemisia annua for managing symptoms of osteroarthritis [1,2], although the most compelling indication for using this herb, is in the treatment of malaria[3,4]. With drug resistance to malaria being an increasingly serious problem, Artemisia annua is a valuable and cost-effective medicine, used both traditionally and by complementary medicine practitioners, to help improve outcomes in malaria patients.

Medsafe submission

Medsafe proposes to change the rules around the availability of Artemisia annua to make *it prescription only.* Excerpts from the Medsafe submission include:

Medsafe identified a potential risk of harm to the liver and a QT prolonging effect with the use of products containing Artemisia annua extract following reports to the Centre for Adverse Reactions Monitoring (CARM). It was noted from many of the CARM reports that consumers stated they were taking this product for arthritis which is a therapeutic purpose.

There is evidence the risks of products containing Artemisia annua outweigh the benefits making it unfavourable for these products to remain unregulated and available for patient self-selection. In addition, there is another artemisinin derivative, artemether, which is classified as a prescription medicine.

Phytomed disagrees with the Medsafe recommendation. We consider that there is insufficient evidence of Artemisia annua, itself, being potentially hepatotoxic or having an unacceptable risk of adverse events (AEs). We believe that the better explanation for the AEs observed will relate to the manufacturing process and/or the purity of the raw material. This will have wider implications than just Artemisia annua.

It is particularly notable, that the 25 adverse event (AE) reports made (up to 30 September 2018) pertaining to Artemisia annua-containing products sold in New Zealand, all relate to two products (Arthrem and Go Arthi-Remedy). It would appear that no consideration of raw material quality or potential contamination or manufacturing-related factors, has been applied by the author(s) of the Medsafe submission.

International evidence for Hepatotoxicity of Artemisia annua

Scientific Literature on Artemisia annua

More than 1000 scientific papers have been published on this medicinal herb and it is mostly known as the origin of a number of 'new generation' anti-malarial drugs (such as artemisinin). Of these papers, 6 relate to the potentially beneficial effects of Artemisia annua, or its phytochemical constituents such as artemisinin or derivatives on liver function[5-11]. These studies suggest that authenticated Artemisia annua leaf may in fact exhibit beneficial effects on liver conditions such as hepatic steatosis and inflammation.

No papers in relation to harmful effects on the liver, appear to have been published in the peer-reviewed scientific literature as at the time of writing.

Reports to International PV Agencies:

EMA:

While we ourselves have not reviewed the European Medicines Agency (EMA) database for AE reports on Artemisia annua, Phytomed engages a QPPV (Qualified Person in Pharmacovigilance) in the EU, who was contacted in February 2018, to look into whether there had been any AEs in relation to this herb in Europe. Her reply received was as follows:

"I have had a look in the EMA portal and also at the MHRA system and I can't find any information on any AEs associated with Artemisia annua (by that name or any of the other 3 names). There are herbal medicines included in the systems, but the fact

that there are no reports means that for the MHRA that they have not ever had a report for that active ingredient, and for the EMA there have been no reports since EudraVigilance was set up.

The only information I can find on either site for Artemisia is an EMA mongraph for Artemesia absinthium and an SmPC on the MHRA website for Artemisia vulgaris for allergy testing - so there is nothing to help I'm afraid."

Given that a wide range of Artemisia annua-containing products are sold in Europe, particularly through TCM practitioners and Chinese medicine clinics, the absence of AE reports to the EMA, is of relevance. Europe has strong regulations in terms of manufacturing standards and Pharmacovigilance requirements.

TGA

A search of the TGA Database of Adverse Event Notifications from 1971 to 2019 for all medicines containing Artemisia annua, found 13 AE reports for a total of 5 different medicines containing this herb. All of these were compound formulations, rather than as an Artemisia annua-only containing product.

Artemisia annua is, however, also sold and used as an individual dried herb or extract for extemporaneous compounding by both TCM practitioners as well as western Naturopaths and Medical herbalists, in that country, as is the case here in NZ.

A copy of the TGA AE report is in the appendix of this submission. Of note is that of the 13 reports received during this 48-year period, only 5 relate to a liver condition according to the MedDRA terms used. These are Ascites (1 case), Hepatitis fulminant (1 case), Hepatomegaly (1 case), Jaundice (1 case) and Hepatic function abnormal (1 case).

Australia has a population that is 5 times that of New Zealand but has similar influences from Asian cultures and traditional medicine (including Artemisia annua) usage. As such, it would be expected to have had many more than 5 cases of hepatotoxicity from products containing this herb over this 48-year period, if Artemisia annual itself was likely to be significantly hepatotoxic. The implication is that it is not Artemisia annua that has caused the AEs in New Zealand.

Summary

In Pharmacovigilance, a signal is information that arises from one or multiple sources, which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

The signal management process covers all steps from detecting signals to recommending action(s) as follows:

- signal detection
- signal validation

- signal analysis and prioritisation
- signal assessment
- recommendation for action
- exchange of information.

The 14 NZ Case reports of hepatotoxicity are of great concern, as drug or herbal medicine-induced liver damage can have serious outcomes. An initial appraisal of EMA and TGA pharmacovigilance data however, as well as the published scientific literature, fails to reveal a significant association between use of Artemisia annua, and liver toxicity. It would therefore seem doubtful that New Zealand's 14 cases were in fact related to the herb itself, given this herb is taken by large numbers of people on a daily basis in many different countries.

It is more likely that deficiencies in the batch of herb(s) used in the manufacture of the specific two brands of proprietary product sold in NZ only, or other manufacturing-related deficits, are responsible for these AE reports.

This is therefore a signal that the specific products for which these AE reports have been received, rather than true unadulterated or uncontaminated Artemisia annua (the herb itself), is likely to be responsible. As such, the assessments and investigations required before being able to recommend an appropriate course of action, should also include a thorough appraisal and testing of the specific products and batches concerned, including their raw materials and the manufacturing processes used.

Whilst reported cases are relatively rare in the published literature, fungal-produced mycotoxins such as aflatoxins and ochratoxins can be associated with liver damage or carcinogenesis [12-13]. The risk of fungal contamination of herbal raw materials is particularly high in low labour-cost countries including many in Africa, where temperatures and humidity are high and where Good Agricultural Practice protocols are not applied during the post-harvest washing or drying, of plant materials.

In recognition of the potential seriousness of such contamination, in the EU there is a requirement for herbal materials included in all licensed herbal medicines to undergo testing to ensure the absence of aflatoxins such as ochratoxins produced by some *Aspergillus spp.* In New Zealand, however, there is no such requirement.

Many raw herbs are imported into New Zealand from low labour-cost countries, and we believe that the Artemisia annua used in proprietary products sold in New Zealand during the period in which these CARM reports were received, was grown in Africa. Poor quality raw material is known to be an issue with certain African countries, and it is therefore essential that the absence of potentially hepatotoxic mycotoxins in this raw material or the products concerned, is verified by Medsafe prior to being able to make a fully informed recommendation to the Medicines Classification Committee.

<u>The Need for Better Regulations in NZ:</u>

As per the Medsafe submission, the present classification of Artemisia annua and its extracts in New Zealand, are dietary supplements. As such they have not been classified and are not

able to make any therapeutic claims. This is materially different to the situation in Australia, where products containing Artemisia annua are complementary medicines, and are listed and notified, on the Australian Register of Therapeutic Goods (ARTG).

Due to many years of successive New Zealand governments shying away from the now urgent need to introduce more appropriate legislation in relation to natural health products/complementary medicines in our country, we are now the only 'developed' country in the world, where there is no requirement for natural health products to be manufactured in a GMP environment. Further, there is no definition of a Herbal Medicine or Complementary Medicine in NZ legislation.

While this situation is likely to have limited Medsafe's apparent jurisdiction in this case, it is the role of a responsible medicines regulator, to be confident it can rule out deficits in the products themselves that may have contributed to this cluster of potentially serious AE events, before advocating to reclassify the herb itself, to a prescription only status.

Finally, Phytomed only supplies Artemisia annua extract to practitioners who have had extensive training in herbal medicine, and we are not aware of pharmacists or doctors having had training in the safe clinical usage of this herb. We would therefore advocate for the establishment of a regulatory system that recognises 'registered medical herbalists', as being able to access a small number of herbal extracts that may have certain safety concerns if sold 'over the counter'. In this context, we support the currently application of the New Zealand Association of Medical Herbalists (NZAMH), for statutory regulation under the Health Practitioners Assurance Act, currently being reviewed by Health Workforce NZ.

We are happy to discuss this as appropriate and expand on any aspect required.

Yours sincerely

Mark Callaghan
CEO

Phil Rasmussen
Technical Director

cc Michael Chamberlain, Board Chair, Phytomed

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Classification of Artemisia annua as a prescription medicine

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Introduction

Medsafe has proposed to the Medicines Classification Committee that the herb Artemisia annua should be classified as a prescription medicine.

Promisia Integrative Ltd opposes this proposal.

Background

Promisia Integrative Ltd (Promisia) is a NZX listed company.

Promisia developed and marketed a joint support product using the extract of the herb Artemisia annua, blended with grape seed oil, in a 150 mg capsule under the brand Arthrem. Arthrem is sold as a dietary supplement. The Artemisia annua seed is sourced from a reliable Swiss supplier and then grown under contract in Tanzania at an altitude of 1,500 meters. The dried leaf is crushed, bagged and shipped to New Zealand where it is subject to carbon dioxide supercritical extraction.

A double-blind placebo controlled trial was undertaken on Promisia's behalf as described on pages 6-9 of the Medsafe submission.

Medsafe has proposed that Artemisia Annua classified as a prescription medicine due to its perceived safety profile.

Artemisia Annua is and has always been a dietary supplement. Promisia strongly oppose the proposal that Artemisia Annua become a prescription medicine as it would prevent many people receiving the benefits that they believe it delivers to them.

Hundreds of thousands of bottles of Arthrem have been sold over the past five years and the reported adverse liver reactions constitute less than 0.007% of all bottles sold (i.e. under 1 in 14,000) – a level the World Health Organization's adverse reactions guidelines consider to be "very rare".

Promisia does not dispute that on rare occasions, adverse reactions associated with the liver have been reported in conjunction with Artemisia Annua.

Attribution of Adverse reactions to Arthrem

Sales of Arthrem in 2016 increased significantly on the back of extensive television advertising and word of mouth from consumers happy with the joint support they experienced from taking Arthrem.

This success was noted by other producers of natural health supplements and three produced a competing product, the largest being go Healthy that produced a product marketed as Go Arthri-Remedy. Go Arthri was a 300mg capsule, mixed with grapeseed oil,

taken once a day. Go-Arthri was marketed to pharmacies as 'the same as Arthrem but cheaper and only one capsule a day'.

The launch of competing products, especially Go Arthri, had a significant negative effect on Arthrem sales. The number of reported adverse reactions also increased significantly when the competing products were released. This information is highlighted on page 2 of Appendix 1 attached to this submission. Appendix 1 is a submission titled 'Credibility of Centre for Adverse Reaction Monitoring (CARM) Reports' and is dated 15 November 2018.

This document was submitted to both Medsafe and CARM along with a request to meet and discuss the report and how the situation could be clarified and how a solution may be developed. Both organizations refused to acknowledge the report or meet to discuss its contents.

For the sake of completeness a copy of the New Zealand Pharmacovigance Centre letter of 19 August 2019 is attached as Appendix 2 to this submission. This letter has as an attachment a report on adverse reactions allegedly attributable to Arthrem up to 30 June 2019. The report gives considerably more detail on each adverse reaction report than the information provided by Medsafe in its submission to this the Medicines Classification Committee. In particular if provides dose levels in some cases but not all cases. This is important information.

We have included below an analysis of each adverse reaction and noted where there are deficiencies in the information that are of sufficient seriousness to cast considerable doubt on the role of Arthrem in these reported cases.

Case No	**Comments**	**Possibly not Arthrem**
110823	The dosage reported by the patient is [redacted] recommended dose which is stated clearly on the bottle.	
119615	This person was taking 9 medicines but only 4 are shown on the NZPC summary. The full list is provided in the Medsafe Alert dated 31 January 2018. A number of these medications are known to have an adverse effect on the liver and any one of them, or a combination of them could have raised hepatic enzyme levels. The stated dose is [redacted] As this information is not provided there is doubt that the product is Arthrem. The reporter is given as [redacted]	
120267	This may well have been Arthrem as competing products were not available. No dosage information is provided and therefore we cannot be certain that if it was Arthrem that it was taken by the consumer as recommended (see 110823 above).	
120445	It is probable that this person was taking Arthrem	

122053	This may well have been Arthrem as competing products were not available. No dosage information is provided	
122052	It is probable that this person was taking Arthrem	
122230	This may well have been Arthrem as competing products were not available. No dosage information is provided and therefore we cannot be certain that if it was Arthrem that it was taken by the consumer as recommended (see 110823 above).	
123150	This may well have been Arthrem as competing products were not available. No dosage information is provided	
124405	The stated dose is [redacted] Arthrem has only been sold in a 150gm capsule.	Yes
124539	No dosage is given and, as competing 300 mg capsule products were available, it is possible that this was not Arthrem.	Yes
124873	The stated dose is [redacted] As this information is not provided there is doubt that the product is Arthrem.	Yes
125218	The stated dose is [redacted] Arthrem has only been sold in a 150gm capsule.	Yes
125378	The stated dose is [redacted] As this information is not provided there is doubt that the product is Arthrem.	Yes
125681	It is probable that this person was taking Arthrem	
125847	The stated dose is [redacted] As this information is not provided there is doubt that the product is Arthrem.	Yes
125947	No information is provided on the dosage or the number of capsules taken per day	Yes
125969	No information is provided on the dosage or the number of capsules taken per day	Yes
125970	No information is provided on the dosage or the number of capsules taken per day	Yes
126905	No information is provided on the dosage or the number of capsules taken per day	Yes
126933	No information is provided on the dosage or the number of capsules taken per day. This person was taking Arthrem, apparently without any adverse reaction, but then switched to Go Arthri-Remedy and started to experience an adverse reaction. It is likely that the [redacted] was the causal factor.	Yes
127117	No dosage is given and, as competing 300 mg capsule products were available, it is possible that this was not Arthrem.	Yes
127445	It is probable that this person was taking Arthrem	
127446	It is probable that this person was taking Arthrem	
127447	The stated dose is [redacted] Arthrem has only been sold in a 150gm capsule.	Yes

127451	This person was taking Arthrem, apparently without any adverse reaction, but then switched to Go Arthri-Remedy and started to experience an adverse reaction. It is likely that the [redacted] was the causal factor.	Yes
127458	It is probable that this person was taking Arthrem	
127475	It is probable that this person was taking Arthrem	
127492	No information is provided on the dosage or the number of capsules taken per day	Yes
127498	The stated dose is [redacted] Arthrem has only been sold in a 150gm capsule.	Yes
127545	The stated dosage is [redacted] This must be an error and brings into dispute the description of the product taken as inaccurate information is provided and it is possible that it was not Arthrem	
127583	The stated dose is [redacted] rthrem has only been sold in a 150gm capsule.	Yes
127632	The stated dose is [redacted] Arthrem has only been sold in a 150gm capsule.	Yes
127666	It is probable that this person was taking Arthrem	
127841	The stated dose is [redacted] Arthrem has only been sold in a 150gm capsule.	Yes
128001	It is probable that this person was taking Arthrem	
128048	It is probable that this person was taking Arthrem	
128413	It is probable that this person was taking Arthrem	
128422	The stated dose is [redacted] Arthrem has only been sold in a 150gm capsule.	Yes

Medsafe has noted that there is a reported adverse reaction (133141) that claimed that a cardiac arrest had been caused by taking Arthrem. There is no evidence in any of the literature that Artemisia annua can cause a cardiac arrest. The fact that a person had a cardiac arrest during the time that they were taking Arthrem does not create causality. We note that the person allegedly took Arthrem from [redacted] and the adverse event was reported by [redacted]

From a total of 38 reported adverse reactions Promisia accepts that 11 were probably attributable to Arthrem. This represents only 29% of reported adverse reactions. The other adverse reactions may well, in our view, be a result of taking a higher dose product.

The CARM reports provided in the submission do not provide information on where the information was collected (Health Professional or member of the public) which is very relevant when evaluation effects on the liver are the issue.

Medsafe state that 23 of the 25 cases were either reported by a health professional or had involved one.

This is misleading as 6 of the 25 cases were reported by [redacted] immediately following the first Medsafe Alert. Most of the actual events occurred up to 12 months earlier and were only reported when promoted by the extensive media coverage that the Medsafe Alert received.

Importance of Dose Levels

It is important to note the result of the clinical trial conducted by Promisia that there was no benefit to trial participants in taking a 300 mg dose and it is for this reason that Promisia produced a 150 mg dose to be taken twice daily, morning and night.

It is clear that there is sufficient uncertainty around dosage, to indicate that Arthrem may well not have been the cause of the adverse reaction. Promisia has requested meetings with Medsafe to discuss this issue but has been rebuffed. Similarly, Promisia has made requests to CARM, both directly and through the Official Information Act, but has not been provided with any additional information.

It is also clear from the graph recording sales of Arthrem and the number of reported adverse reactions that the number of reported adverse reactions coincided with the sale by three competitors of a single 300 mg dose of Artemisia annua.

CARM data collected on Arthrem (which is used as justification in the Medsafe submission) is inaccurate and provides clear evidence that the collection process and the information collected is either incorrect or points to another cause or product for the adverse reactions. Medsafe has ignored the document Appendix 1 supplied by Promisia and has not supported the process of ensuring the accuracy of the information collected for CARM reports. This attitude by both Medsafe and CARM may have, or might well have, negative implications for other product producers.

The producers of the 300mg capsules withdrew their products from the market at the time of the Medsafe Alert in February 2018.

Proposed Lower Dose Product

Following the February 2018 Medsafe Alert Promisia considered how an Artemisia annua product could continue to be made available with a very low risk of adverse reactions. It is noted that nothing is 100% safe, be it a natural product or a registered medicine. Some people are allergic to their mother's milk!

The in-vitro trial undertaken in January 2015 by Trinity Bioactive Ltd indicated that the impact on inflammatory makers of a 75 mg dose of Artemisia annua was similar to a 150 mg dose. In June 2018 Promisia approached Medsafe to discuss the company's proposal to launch a new Arthrem product that would consists of a lower dose of Artemisia annua, being a 75mg capsule that would be taken twice daily, morning and night. This 'New Formula Arthrem' would replace the current Arthrem over a period of a few months as stock of Arthrem sold out from pharmacies.

The reaction of Medsafe was that it would not meet to discuss this proposal and that the company could not use the brand 'Arthrem'.

Despite attempts to meet with Medsafe to try to resolve the use of a natural product where it is clear that a higher rather than lower dose may be responsible for the majority of the reported adverse reactions, these efforts have been rebuffed.

Medsafe has shown no interest in the fact that many people did receive enhanced joint support from taking Artemisia annua and a large number continue to take the product today without any adverse effect.

Comment on Other Matters in the Medsafe Proposal

In item 12, Labelling or Draft Labelling, on page 5 of its proposal, Medsafe states that it does not have access to a label sample for any Artemisia annua product. Promisia disputes this statement. Medsafe has taken a very close interest in Arthrem and it beggars believe that it has not undertaken an exhaustive investigation and review of all aspects of the product. It will have samples of the product and the label on the bottle.

As noted earlier, Arthrem has always been marketed as a dietary supplement. It has never been promoted as a medicine. Medsafe recommends that producers of dietary supplements use and experienced consultant to assist them in the preparation of all marketing and product support material, including labels. The consultant recommended by Medsafe is the Therapeutic Advertising Pre-Vetting Service, known as TAPS. Promisia has submitted every piece of labelling, marketing support and advertising material, including television and radio advertisements, to TAPS for review. This pre-vetting has been at a cost of many thousands of dollars in an endeavour to ensure that all activities around Arthrem have been compliant with New Zealand requirements. Promisia has relied on the advice of TAPS for compliance.

Medsafe must also remove any refence to Artemether in relation to Artemisia Annua. Artemether is a synthetic derivative with known side effects.

In addition, Artemisinin which is extracted for the treatment of Malaria is a product obtained by solvent extraction. Artemisia Annua extract is a natural product, extracted using only pressure and CO2. Comparisons between the extracts highlight significant differences.

Proposed Alternative Resolution

Medsafe's submission to the Medicines classification committee wishes to classify all products containing Artemisia Annua at any dose as a prescription medicine.

Promisia believes this to be completely unnecessary and believe that a reduction in dose to 75mg twice daily will address the safety issues.

Public safety is extremely important. Promisia supports the view that a higher rather than lower dose of Artemisia annua may increase the level of adverse reaction. Promisia has also proposed producing a lower dose product to address this issue.

A more productive and even-handed approach is to reach agreement with the sector that the Artemisia annua content is any dietary supplement should not exceed, say, 75 mg per capsule and that the maximum dose must not exceed 150 gm per day.

Such an outcome would demonstrate a collaborative approach to addressing a safety issue without resorting to a heavy handed approached adopted by Medsafe to date. We urge the Medicines Classification Committee to reject the proposal by Medsafe to designate Artemisia annua as a medicine. Further, we request that it directs Medsafe to meet with the natural products sector to agree a dosage for Artemisia annua that enables users to get the benefits of the plant while also protect those people with a higher sensitivity to the herb.

Conclusion

The proposal to use the classification as a medicine of a natural product that has been used for centuries is an extreme measure and sets a dangerous precedent for other plants and plant extracts.

Promisia cannot see how a plant extract can be described as a medicine as the extract can vary from season to season and by location. The extraction process used may also produce a different outcome from another extraction process. It is a requirement of a medicine that every dose is the same and this outcome will be extremely difficult to achieve in the case of any plant extract.

Medsafe claim that the risk to the liver with the use of products containing Artemisia Annua outweighs the modest benefits in maintaining and supporting joint health and mobility. Promisia disagrees and suggests that requirements are put in place regarding the origin of the extracts used and a reduction in the dose to a maximum of 75mg twice daily. This will address and eliminate their perceived risks while making the product available to the many people who derive a benefit from the herb.

Appendix 1

Credibility of Centre for Adverse Reaction monitoring (CARM) Reports. 15 November 2018

The CARM reports supplied by the NZ Pharmacovigilance Centre are, in the view of Promisia Integrative Ltd ("PIL", "Promisia" or "the Company") incomplete and inaccurate. This raises questions as to the level of credibility that can be attached to these reports and whether they can be relied upon by Medsafe to base its assumptions and consequential decisions and actions.

Following the original Alert on the 15 February 2018, there were a number of new reports concerning the alleged adverse reactions to Arthrem. This would be expected, based on both the release of the Alert and the media coverage that followed the Alert.

Medsafe is aware that Promisia's product Arthrem has a recommended dose of one 150mg capsule taken twice a day, morning and night. The competing products released in early 2017 all had a recommended dose of one 300mg capsule taken once daily.

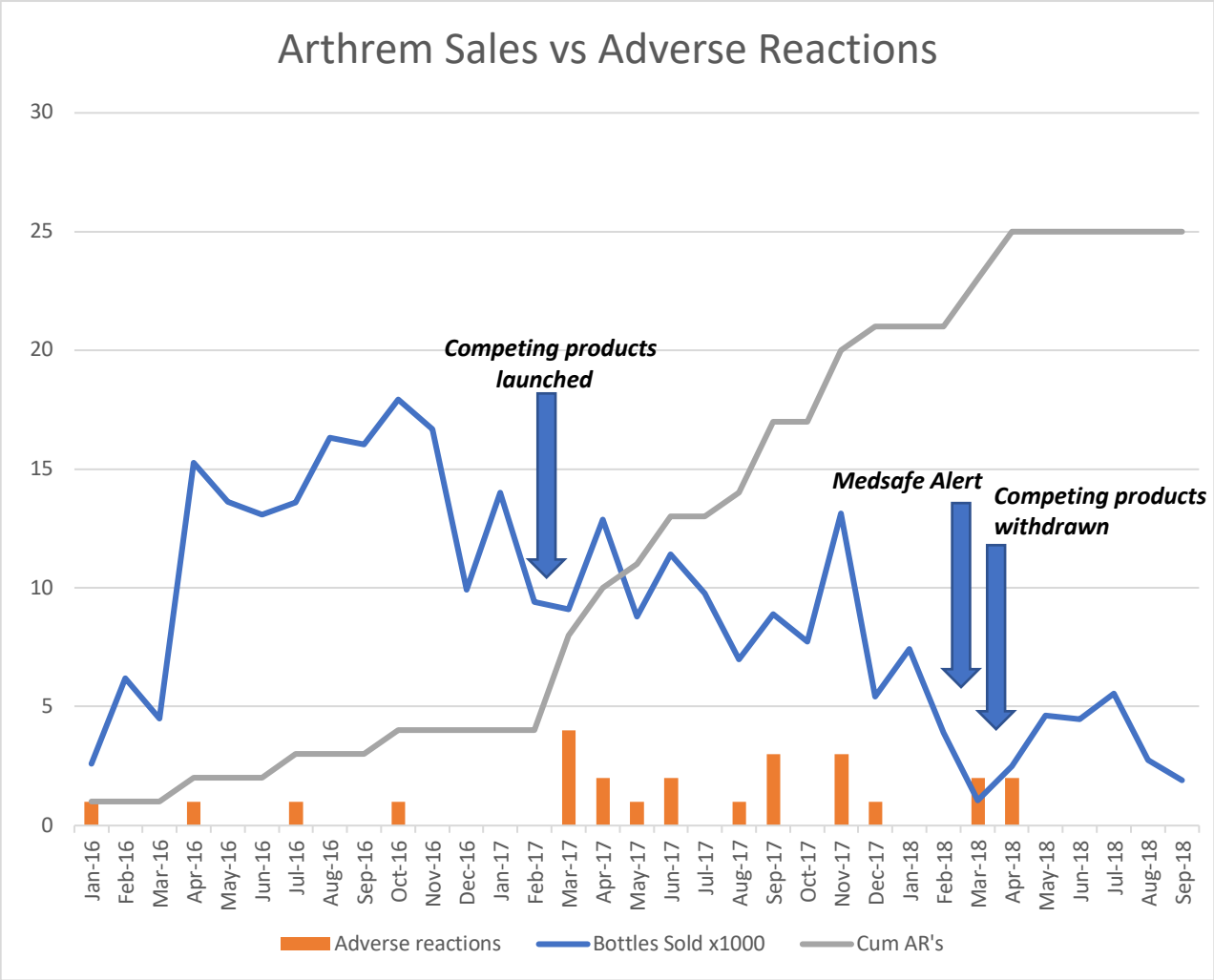
Immediately following the Medsafe Alert, Promisia's actions were to add warning labels to every bottle of Arthrem and provide more comprehensive education and training to pharmacy staff and members of the public who purchased Arthrem.

The main competitor to Arthrem was Go-Arthri Remedy, produced as part of the Go Healthy range. This product was sold mainly through pharmacies at a lower price than Arthrem and with significant marketing, including television advertising, and instore sales support. Pharmacy staff were told that Go-Arthri Remedy was "the same as Arthrem but in a single dose at a lower price".

The graph below tracks the monthly bottle sales of Arthrem, the actual monthly reported adverse reactions, and the cumulative number of reported adverse reactions. It is clear that the introduction of competing products in February 2017 had an immediate impact in the form of both a reduction in the sales of Arthrem and the increase in the number of adverse reactions. It follows that the number of reported adverse reactions cannot be attributed to Arthrem as claimed by Medsafe.

Following the Medsafe Alert Go Healthy withdrew Go-Arthri Remedy from the market, which had the immediate effect of lowering the number of adverse reactions. Since the issue of the Medsafe Alert and the withdrawal of Go-Arthri Remedy there have been only four reported adverse reactions. Those four reactions may have been caused by Go- Arthri Remedy while the individual completed taking an existing supply of that product.

It is clear that the adverse reactions increased by a factor of 6 as soon as GO-Arthri Remedy was released for sale in New Zealand and dropped immediately following its withdrawal in March 2018. It is important to note that there have been no reported adverse reactions in the period from the end of April 2018 to September 2018.



Safety testing and clinical trials on Arthrem confirm that the most suitable dose is 2 x 150mg taken as one 150mg dose in the morning and another in the evening. Competing products promoted a single 300mg dose per day which was not recommended in the testing of Arthrem. The CARM reports show dosages consistent with Go-Arthri Remedy use rather than Arthrem. This is discussed below.

Genericization

Genericization is a phenomena where a product or process is so successful that it becomes the default term to describe the product or action, even if it uses another product. Examples include 'doing the hoovering' and 'to Xerox an article etc.' Promisia believes that a significant level of genericization occurred with Arthrem.

Many customers using Arthrem were persuaded to buy a competing product on the basis that "it was the same as Arthrem" but at a lower price and required taking only one capsule a day rather than two. In the minds of many purchasers they had been taking Arthrem and if the pharmacy said that the new cheaper and one capsule a day product was "the same as Arthrem" then they considered that they were still taking Arthrem.

This view is supported by the detail in the CARM reports of adverse reactions where the parties lodging the reaction detailed that they were taking one capsule per day. The Arthrem recommended dose is one capsule twice a day. There is therefore strong grounds to conclude that the adverse reaction has been attributed incorrectly to Arthrem.

Source of Artemisia annua extract

Promisia produces its own Artemisia annua extract. Seed is sourced from a reputable Swiss seed company. The seed is planted out at a contracted farm in Tanzania where dried leaf is harvested at maturity. The dried leaf is transported to New Zealand and processed by a CO2 extraction company in New Zealand. The final extract is tested to ensure that it is free of impurities and contamination.

Competing product uses an extract from China which is uncontrolled and untested.

Detailed Analysis of CARM Adverse Reaction Reports

Timing of Adverse Reactions

Of the 25 adverse reactions collected by CARM, 21 occurred before the Medsafe Alert in February 2018 and while competing products were still on the market (although 8 were reported to CARM after the Alert). Some of the reported adverse reactions made after the Alert occurred as long as 12 months prior to the Alert. It is interesting that some people (mostly members of the public) only reported an adverse reaction after the publicity generated by the Alert. The reliability of adverse reactions reported after a significant delay, by members of the public without support of professional medical expertise, has to be in doubt.

Analysis of CARM reported Adverse Reactions

A detailed review of the information provided by CARM to Medsafe, and Promisia, allows these reported adverse reactions to be split into various categories.

a) Definitely not Arthrem

Two of the 25 reports name GO-Arthri Remedy as the product the person was taking when the adverse reaction occurred, not Arthrem. In fact one patient reported that they did not have an adverse reaction while taking Arthrem but only when they started taking GO-Arthri Remedy.

b) Probably not Arthrem

Four of the 25 claim the dose they were taking was [redacted]. The recommended dose for Arthrem is 150mg which suggests the patient was not taking Arthrem but a competing product.

Five of the 25 reports claim only [redacted]. The competing products recommend one capsule per day whereas the recommended dose of Arthrem is one capsule twice daily. If the patient reported that they took [redacted] it would indicate that the patient was not taking Arthrem.

Based on the information provided by CARM, as many as 11, or 44% of reported adverse reactions, were probably not or definitively not Arthrem.

c) No dose information supplied

Nine of the 25 reports have no information about dose. This information is critical in establishing which product the patient was actually taking.

If no dosage information is provided by the patient or his or her medical practitioner then the claim that they were taking Arthrem cannot be accepted on an unqualified basis. As noted above, the genericisation of Arthrem may mean, based on the information in a) to c) above, at least 44% of these nine reported adverse reactions, being four instances, were probably not related to Arthrem but to a competing product.

Therefore it is probable that 15, or 60%, of the reported adverse reactions were not related to Arthrem but to a competing product.

d) Report not supported by medical expertise

Six of the 25 reports were made by [redacted] who would not have the required medical knowledge to evaluate the symptoms they claim to have had. Those individuals may not have reported any medications they may have been taking which are known to affect liver function.

e) Person taking medications known to affect the liver

Twelve of the individuals reporting an adverse reaction to Arthrem reported that they were taking medication. Arthrem is not a medication, it is a dietary supplement. Ten of those people were taking another medication that is also known to have a negative impact on liver function. It is not clear if that possibility that the adverse reaction was caused by those medications had been considered by either CARM or Medsafe.

It is extremely hard to believe that many patients in their 60s, 70s and 80s would not be taking any either one or more medicines or dietary supplements as well as Arthrem. It is Promisia's view that a person who has chosen to take Arthrem may well be taking some form of medication, especially pain medication if they are suffering from joint pain.

However, 15 of the 25 reported adverse reactions claim that Arthrem is the only supplement or medicine they were taking. This is questionable and brings into doubt the accuracy of the CARM reporting system.

f) Adverse reactions occurring since February 2018

Since the release of the Medsafe Alert in February 2018 there are only four adverse reaction reports relating to the period post February 2018. Three relate to an increase in liver enzymes detected in blood tests and, as this is not uncommon, there is no proof that it was caused by Arthrem.

The fourth relates to Hepatic cirrhosis in an 81 year old man. Promisia has undertaken a literature search and there is no evidence that Artemisia annua, and therefore Arthrem, can cause cirrhosis. Medsafe appears to have accepted the CARM report without question and without any investigation into the person's medical history. The patient may be a heavy consumer of alcohol, which is one of the three primary causes of cirrhosis of the liver. He was also taking two medications that are known to cause liver issues.

Summary

There is clear evidence that the CARM reporting process is flawed due to the inadequacy and inaccuracy of the information collected. It cannot be relied on for the purpose of creating Alerts and certainly questioning the safety of specific products such as Arthrem.

Medsafe's update is intentionally misleading. It gives a misleading impression that there have been 11 more adverse events following the previous Alert when the truth is that 8 of these reports relate to the period covered by the original Alert.

The incidence and nature of reported adverse reactions since February 2018 does not warrant or justify the issue of another Alert.

The reporting of adverse reactions has stopped since competing high dose products competing with Arthrem have been withdrawn from the market.

The evidence supports the view that the majority of reported adverse reactions related to products in the form of a single 300mg capsule rather than a 150 mg capsule taken twice a day. Further, Promisia believes that it is being targeted unfairly and on a prejudicial basis by Medsafe without sufficient evidence to support Medsafe's actions.

There is no justification at all for the draft Alert to refer to Arthrem in the title or to focus on Arthrem when the draft Alert then goes on to refer to other products on the market containing *Artemisia annua*.

Promisia has been careful to provide warnings on its bottle label and marketing material warning people with specific and general conditions not to take the product. An example of this warning is detailed on page 11 of the Medsafe submission.

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19 August 2019

Rene de Wit
Chief Executive Officer
Promisia Limited
22 Panama Street
WELLINGTON 6011

Dear Rene

In response to your letter of 29 January 2019, following is clarification of the information detailed on the CARM report listings provided to your Company.

Dose:
The dose indicated is the daily dose. For those reports where [redacted] this is the amount taken per day. Other reports simply indicate [redacted] capsules per day and this is shown as [redacted] DF where DF stands for '*Dosage Form'.*

Genericization:
Your comment is noted however in the case of assessments made at CARM, in particular the Arthrem case assessments, these have been undertaken by two long-standing pharmacovigilance medical specialists who have been working in this field for an extensive number of years.
The Reporter's reference to Arthrem as the product name is accepted as correct.

Dates:
All dates indicated on the CARM report listings under the fields BEGAN, ENDED, and Onset are in the format of ddmmyy. If these dates are only partial such as missing the day or month then the missing information is shown as '00'.

If no dates are provided but the duration is indicates as "days" or " few weeks" etc then:
Short Term use (S TERM) is indicated when treatment is indicated as less than 3 months
Long Term use (L TERM) is indicated when treatment is indicated as more than 3 months
If there is no indication of dates or duration of treatment then the field is blank.

Persons taking medications known to affect the liver:
Our Medical Assessors consider many factors when assessing cases which includes other medications and co-morbid conditions.

I have provided an updated listing of the Arthrem reports received by CARM up to 30 June 2019 for your information along with our Caveat Document which will assist with the understanding of the data.

Janelle Ashton
Manager Information Systems

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Report Title: **Arthrem**

Prepared by: **New Zealand Pharmacovigilance Centre**

Period Covered: The detail in this document includes all cases up to 30 June 2019

Summary: Reports received by NZPhvC as at 30 June 2019 = **45**

Table 1: Reports received per year up to 30/06/2019

Date	No. of Reports	Cumulative
2014	1	1
2016	6	7
2017	13	20
2018	21	41
2019 – 30 June	4	45

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CAVEAT DOCUMENT

Accompanying statement to data released from the

NEW ZEALAND CENTRE FOR ADVERSE REACTIONS MONITORING

The Centre for Adverse Reactions Monitoring (CARM) has only limited details about each suspected adverse reaction contained in its Database. It is important that the limitations and qualifications which apply to the information and its use are understood.

The data made available represent the collection of spontaneous reports in the CARM database associated with therapeutic products/vaccines granted regulatory approval for use in New Zealand. The database also includes non-regulated products such as Natural Health Products and Dietary Supplements.

Reports have been submitted to the Centre since April 1965 and in many instances describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. This level of reporting is due to CARM encouraging reporters to report events they suspect may be associated with a pharmaceutical product/vaccine/other products irrespective of whether or not they believe it was the cause. CARM accepts all reports and proof of causality is not required when submitting a report to CARM. Coincidental events that may be unrelated to pharmaceutical product/vaccine/other products exposure may be reported. This is particularly possible when the product has widespread use, or is used in targeted strategies such as vaccination campaigns.

In most instances it cannot be proven that a pharmaceutical product or ingredient is the cause of an event in the Database. Reports vary in quality, completeness and detail and may include detail that is incorrect. Consequently, a report in the CARM database of an event does not confirm that the product/vaccine caused the event.

The volume of reports for a particular product may be influenced by the extent of use of the product, publicity, nature of reactions and other factors which vary over time and from product to product. It is generally accepted internationally that systems such as CARM are subject to under-reporting which may result in scant reports for events perceived by the reporter to be minor or well recognised, whilst more serious or unexpected events are possibly more likely to be reported, even if they are coincidental. Moreover, no information is provided on the number of patients exposed to the product.

The data contained in these tables are further subject to ongoing internal quality controls, review and updating and therefore may be subject to change, particularly if follow-up information is received.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between products, may be misleading. Any use of this information must take into account at least the above. Although this information is now released, it is strongly recommended that prior to any use of such information, CARM is contacted for interpretation.

Any publication, in whole or in part, of the obtained information must have published with it a statement:

(i) of the source of the information

(ii) that the information is not homogenous at least with respect to origin or likelihood that the product/vaccine caused the adverse reaction,

(iii) that the information does not represent the opinion of the NZPhvC or CARM.

Director
New Zealand Pharmacovigilance Centre

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Arthrem Case Reports – Total

REPORT	ORIGIN	DATE	REACTIONS		DRUGS	ROUTE	DOSE/UNIT/FREQ	BEGAN	ENDED	AGE	SEX	OUTCOME
110823	[redacted]	MAR2014	NAUSEA ANOREXIA DIARRHOEA	*	ARTHREM	[redacted]	[redacted]	[redacted]		64	F	[redacted]
119615	[redacted]	FEB2016	HEPATIC ENZYMES INCREASED	*	ARTHREM PANTOPRAZOLE ATORVASTATIN CILAZAPRIL/HYDROCHLOROTHIAZIDE FLUOXETINE	[redacted]	[redacted]	[redacted]	[redacted]	71	M	[redacted]
120267	[redacted]	APR2016	RASH ERYTHEMATOUS PRURITUS	*	ARTHREM OMEPRAZOLE IBUPROFEN ATORVASTATIN AMILORIDE/HYDROCHLOROTHIAZIDE	[redacted]	[redacted]		[redacted]	82	F	[redacted]
120445	[redacted]	APR2016	HEPATIC ENZYMES INCREASED ABDOMINAL PAIN NAUSEA FEVER	*	ARTHREM DILTIAZEM CILAZAPRIL NORTRIPTYLINE PARACETAMOL	[redacted]	[redacted]	[redacted]	[redacted]	48	F	[redacted]
121953	[redacted]	AUG2016	ERYTHEMA	*	ARTHREM	[redacted]	[redacted]	[redacted]		54	M	[redacted]
122052	[redacted]	SEP2016	HEPATITIS JAUNDICE PRURITUS	*	ARTHREM	[redacted]	[redacted]		[redacted]	54	F	[redacted]
122230	[redacted]	SEP2016	QT PROLONGED	*	ARTHREM	[redacted]		[redacted]		76	F	[redacted]

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REPORT	ORIGIN	DATE	REACTIONS		DRUGS	ROUTE	DOSE/UNIT/FREQ	BEGAN	ENDED	AGE	SEX	OUTCOME
123150	[redacted]	JAN2017	JAUNDICE PRURITUS HEPATITIS	*	ARTHREM * TURMERIC FISH OIL GLUCOSAMINE IBUPROFEN	[redacted]		[redacted]		76	F	[redacted]
124405	[redacted]	MAY2017	HEPATIC FUNCTION ABNORMAL JAUNDICE PRURITUS	*	ARTHREM MESALAZINE	[redacted]	[redacted]	[redacted]		67	F	[redacted]
124539	[redacted]	MAY2017	HEPATIC ENZYMES INCREASED JAUNDICE	*	ARTHREM URSODEOXYCHOLIC ACID CHOLECALCIFEROL	[redacted]	[redacted]	[redacted]		72	F	[redacted]
124873	[redacted]	JUN2017	HEPATITIS CHOLESTATIC JAUNDICE NAUSEA FEVER	*	ARTHREM FELODIPINE	[redacted]	[redacted]	[redacted]		55	F	[redacted]
125218	[redacted]	JUL2017	FUZZY HEAD CONFUSION	*	ARTHREM DOXAZOSIN INSULIN NEUTRAL/ISOPHANE CILAZAPRIL OMEPRAZOLE	[redacted]	[redacted]	[redacted]		82	M	[redacted]
125378	[redacted]	JUL2017	HEPATITIS	*	ARTHREM ATORVASTATIN OMEPRAZOLE CANDESARTAN	[redacted]	[redacted]	[redacted]		62	M	[redacted]
125681	[redacted]	AUG2017	FEVER	*	ARTHREM	[redacted]	[redacted]		[redacted]	71	F	[redacted]

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125847	[redacted].	SEP2017	HEPATIC FUNCTION ABNORMAL JAUNDICE	* ARTHREM FISH OIL ASCORBIC ACID	[redacted]	[redacted]	[redacted]		66	F	[redacted]
125947	[redacted].	SEP2017	NAUSEA VOMITING HEPATIC ENZYMES INCREASED	* ARTHREM	[redacted]		[redacted]		64	F	[redacted]
125969	[redacted]	SEP2017	JAUNDICE HEPATIC FUNCTION ABNORMAL	* ARTHREM * MELATONIN METOPROLOL DOXEPIN ACETYLSALICYLIC ACID	[redacted]		[redacted]		76	F	[redacted]
125970	[redacted]	SEP2017	JAUNDICE HEPATIC FUNCTION ABNORMAL RASH ANOREXIA ABDOMINAL PAIN	* ARTHREM ACETYLSALICYLIC ACID CILAZAPRIL DOXAZOSIN	[redacted]	[redacted]	[redacted]		77	M	[redacted]
126905	[redacted]	DEC2017	JAUNDICE HEPATIC ENZYMES INCREASED	* ARTHREM METOPROLOL	[redacted]	[redacted]	[redacted]		55	M	[redacted]
126933	[redacted]	DEC2017	JAUNDICE HEPATIC ENZYMES INCREASED	* ARTHREM * GO ARTHRI-REMEDY	[redacted]		[redacted]		71	F	[redacted]
127117	[redacted]	JAN2018	DIARRHOEA FEVER VOMITING HYPOTENSION NAUSEA	* ARTHREM ANTIHISTAMINES UNCLASSIFIED PARACETAMOL IBUPROFEN TRAMADOL	[redacted]		[redacted]		41	F	[redacted]

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127445	[redacted]	FEB2018	HEPATIC FUNCTION ABNORMAL JAUNDICE PRURITUS FAECES PALE ANOREXIA	* ARTHREM	[redacted]	[redacted]	[redacted]		65	M	[redacted]
127446	[redacted]	FEB2018	URINE DISCOLOURATION VISION ABNORMAL	* ARTHREM MAGNESIUM	[redacted]	[redacted]	[redacted]		57	F	[redacted]
127447	[redacted]	FEB2018	JAUNDICE VOMITING HEPATIC ENZYMES INCREASED ANOREXIA ABDOMINAL PAIN	* ARTHREM PARACETAMOL/CODEINE DICLOFENAC	[redacted]	[redacted]	[redacted]		60	M	[redacted]
127451	[redacted]	FEB2018	HEPATIC ENZYMES INCREASED	* ARTHREM * GO ARTHRI-REMEDY	[redacted]	[redacted]	[redacted]		57	F	[redacted]
127458	[redacted]	FEB2018	URTICARIA	* ARTHREM	[redacted]	[redacted]	[redacted]		52	M	[redacted]
127475	[redacted]	FEB2018	JAUNDICE HEPATIC ENZYMES INCREASED PRURITUS PURPURA HAEMATURIA	* ARTHREM	[redacted]	[redacted]	[redacted]		64	F	[redacted]
127492	[redacted]	FEB2018	JAUNDICE PRURITUS HEPATIC ENZYMES INCREASED TIREDNESS	* ARTHREM	[redacted]		[redacted]		69	F	[redacted]

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REPORT	ORIGIN	DATE	REACTIONS		DRUGS	ROUTE	DOSE/UNIT/FREQ	BEGAN	ENDED	AGE	SEX	OUTCOME
127498	[redacted]	FEB2018	INFLUENZA-LIKE SYMPTOMS URTICARIA VOMITING TASTE METALLIC SYNCOPE	*	ARTHREM VITAMIN B COMPLEX FISH OIL MAGNESIUM CRANBERRY EXTRACT	[redacted]	[redacted]	[redacted]	[redacted]	69	F	[redacted]
127545	[redacted]	MAR2018	CONJUNCTIVAL CONGESTION PRURITUS	*	ARTHREM WARFARIN METOPROLOL ALLOPURINOL	[redacted]	[redacted]	[redacted]	[redacted]	83	M	[redacted]
127583	[redacted]	MAR2018	HEADACHE PRURITUS ABDOMINAL PAIN CHILLS	*	ARTHREM MAGNESIUM ASCORBIC ACID	[redacted]	[redacted]	[redacted]	[redacted]	51	F	[redacted]
127632	[redacted]	MAR2018	HEPATIC ENZYMES INCREASED	*	ARTHREM METOPROLOL DONEPEZIL PANTOPRAZOLE ATORVASTATIN	[redacted]	[redacted]	[redacted]	[redacted]	93	F	[redacted]
127666	[redacted]	MAR2018	DERMATITIS LICHENOID PHOTOSENSITIVITY REACTION	*	ARTHREM	[redacted]	[redacted]	[redacted]	[redacted]	77	M	[redacted]
127841	[redacted]	MAR2018	HEPATIC FUNCTION ABNORMAL	*	ARTHREM ATORVASTATIN FELODIPINE ACETYLSALICYLIC ACID TIOTROPIUM BROMIDE	[redacted]	[redacted]	[redacted]	[redacted]	71	M	[redacted]
128001	[redacted]	APR2018	HEPATIC ENZYMES INCREASED	*	ARTHREM	[redacted]	[redacted]	[redacted]	[redacted]	69	M	[redacted]

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128048	[redacted]	APR2018	HEPATIC CIRRHOSIS ENCEPHALOPATHY	*	ARTHREM CILAZAPRIL METOPROLOL ALLOPURINOL THYROXINE	[redacted]	[redacted]	[redacted]	[redacted]	81	M	[redacted]
128413	[redacted]	MAY2018	HEPATIC ENZYMES INCREASED	*	ARTHREM	[redacted]	[redacted]	[redacted]	[redacted]	83	F	[redacted]
128422	[redacted]	MAY2018	JAUNDICE HEPATITIS CHOLESTATIC PRURITUS	*	ARTHREM	[redacted]	[redacted]	[redacted]	[redacted]	86	F	[redacted]
130587	[redacted]	OCT2018	HEPATIC ENZYMES INCREASED JAUNDICE ANOREXIA NAUSEA	*	ARTHREM HYDROCORTISONE BUTYRATE	[redacted]	[redacted]	[redacted]	[redacted]	65	F	[redacted]
130741	[redacted]	NOV2018	GAMMA-GT INCREASED	*	ARTHREM VENLAFAXINE	[redacted]	[redacted]	[redacted]	[redacted]	68	F	[redacted]
130819	[redacted]	NOV2018	HEPATIC ENZYMES INCREASED	*	ARTHREM CYPROTERONE ACETATE PROPRANOLOL AMITRIPTYLINE BUDESONIDE/EFORMOTEROL	[redacted]	[redacted]	[redacted]	[redacted]	62	F	[redacted]
131411	[redacted]	JAN2019	HEPATITIS ABDOMINAL PAIN	*	ARTHREM	[redacted]	[redacted]	[redacted]	[redacted]	57	M	[redacted]

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131808	[redacted]	FEB2019	RENAL FAILURE CHRONIC	*	ARTHREM ALENDRONATE	[redacted]	[redacted]	[redacted]	[redacted]	72	F	[redacted]
132205	[redacted]	MAR2019	GAMMA-GT INCREASED	*	ARTHREM MAGNESIUM FISH OIL CO-ENZYME Q10 ASCORBIC ACID	[redacted]	[redacted]	[redacted]	[redacted]	68	M	[redacted]
133141	[redacted]	MAY2019	QT PROLONGED CARDIAC ARREST	* *	ARTHREM CITALOPRAM BENDROFLUAZIDE GLUCOSAMINE + CHONDROITIN MAGNESIUM	[redacted]	[redacted]	[redacted]	[redacted]	57	F	[redacted]

Journal of Inflammation Research

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ORIGINAL RESEARCH

An extract of the medicinal plant *Artemisia annua* modulates production of inflammatory markers in activated neutrophils

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Purpose: To investigate the ability of a commercial extract from the medicinal plant *Artemisia annua* to modulate production of the cytokine, tumor necrosis factor-alpha (TNF-α), and the cyclooxygenase (COX) inflammatory marker, prostaglandin E_2 (PGE_2) in activated neutrophils.

Methods: Neutrophils were harvested from rat whole blood and cultured in the presence of plant extract or control samples. Neutrophils, except unactivated control cells, were activated with 10 μg/mL lipopolysaccharide (LPS). The cells were cultured with a range of different concentrations of the *A. annua* extracts (400–1 μg/mL) and artemisinin (200 and 100 μg/mL) and the supernatants were then tested by enzyme-linked immunosorbent assay (ELISA) for the concentrations of TNF-α and PGE_2. Each sample was assayed in triplicate. Positive controls with an inhibitor were assayed in triplicate: chloroquine 2.58 and 5.16 μg/mL for TNF-α, and ibuprofen 400 μg/mL for PGE_2. An unsupplemented group was also assessed in triplicate as a baseline control.

Results: Neutrophils were stimulated to an inflammatory state by the addition of LPS. *A. annua* extract significantly inhibited TNF-α production by activated neutrophils in a dose-dependent manner. There was complete inhibition by the *A. annua* extract at 200, 100, and 50 μg/mL (all $P \leq 0.0003$). At *A. annua* extract concentrations of 25, 10, and 5 μg/mL, TNF-α production was inhibited by 89% ($P < 0.0001$), 54% ($P = 0.0002$), and 38% ($P = 0.0014$), respectively. *A. annua* 1 μg/mL did not significantly inhibit TNF-α production (8.8%; $P > 0.05$). Concentrations of 400, 200, and 100 μg/mL *A. annua* extract significantly inhibited PGE_2 production by 87% ($P = 0.0128$), 91% ($P = 0.0017$), and 93% ($P = 0.0114$), respectively.

Conclusion: An extract of *A. annua* was shown to be a potent inhibitor of TNF-α and a strong inhibitor of PGE_2 production in activated neutrophils at the concentrations tested. Further studies are warranted with this promising plant extract.

Keywords: in vitro, TNF-α, COX-2, PGE_2, artemisinin, Arthrem

Introduction

Much recent attention has been given to traditional medicines and natural products with potential and promising anti-inflammatory properties.[1–4] However, much of the evidence is minimal or anecdotal, and it is clear that more research is needed in this area.[2]

The medicinal plant *Artemisia annua* L. (Asteraceae) is native to the People's Republic of China but has been introduced and grows wild throughout Asia, North America, and Europe, and is now broadly cultivated for medicinal purposes.[5] *A. annua* has been used as a medicinal herb for more than 2,000 years.[6] Traditional uses of the plant include as an antimalarial, a food additive, an anti-inflammatory, and to treat

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hemorrhoids, lice, and boils.[2] Texts on Chinese herbal medicines, written as early as 200 AD, also reported that it relieved joint pain.[5]

In the 1970s, researchers in the People's Republic of China identified one of the main components of *A. annua*; a sesquiterpene lactone, artemisinin.[5,6] Artemisinin-based therapy is one of the most effective agents for the prevention and treatment of malaria and has been used successfully to treat millions of people worldwide.[7–11] The mechanism of action against malaria is still debated, even though a number of potential targets have been proposed, such as alkylation of heme or proteins, inhibition of a parasite gene, or damage to the parasite's membrane.[12] The compounds in *A. annua* appear to have other bioactive properties and may have broader anti-disease applications beyond the treatment of malaria.[13]

Artemisinin appears to have anti-inflammatory properties, probably due to the inhibition of inflammatory factors and mediators such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-1β, and nitric oxide.[14,15] Other antimalarial drugs, especially quinine derivatives, are standard therapies for the treatment of rheumatoid arthritis and systemic lupus erythematosus, where they appear to have both disease-modifying and anti-inflammatory effects.[16]

The aim of this study was to investigate the ability of an extract of *A. annua* to modulate production of the cytokine TNF-α in activated neutrophils. Preliminary investigations were also conducted on the ability of *A. annua* to modulate production of the cyclooxygenase (COX) inflammatory marker, prostaglandin E_2 (PGE_2) in activated neutrophils. These commonly studied markers were chosen as they are known to be produced by neutrophils from many species and can also be easily studied and quantified using well-documented in vitro assays.

Materials and methods

Plant material

A commercial supercritical carbon dioxide extract of *A. annua* was used in the assays. The extract is used in Arthrem™ capsules (Promisia Integrative Ltd, Wellington, New Zealand), a dietary supplement for joint support. Commercially available artemisinin capsules (Super Artemisinin; NutriCology, Alameda, CA, USA) were also tested.

Cell culture

Rat blood was taken by cardiac puncture of animals under an animal ethics protocol approved by the Animal Ethics Committee, University of Otago, Wellington, New Zealand. Blood was collected in an anticoagulant (ethylenediaminetetraacetic acid) tube, inverted several times, and kept at 18°C–22°C. Polymorphprep™ (Axis-Shield, Oslo, Norway) 2.5 mL was added to each centrifuge tube, overlayered with 7.0 mL whole blood, and centrifuged at 500 *g* for 30 minutes at 20°C. After centrifugation, the polymorphonuclear fraction was suspended with Hank's Balanced Salt Solution (HBSS) and centrifuged at 125 *g* for 5 minutes at 4°C. The supernatant was discarded and the cell pellet was resuspended, washed with HBSS, and centrifuged at 125 *g* again. The supernatant was discarded and the cell pellet was resuspended in RPMI-1640 medium (Gibco, Auckland, New Zealand). The cell number was counted and the concentration adjusted to 5.0×10^6 cells/mL with RPMI-1640 medium. The cell suspensions containing isolated neutrophils were kept on ice for up to 10 minutes until used in the assays.

Experimental assays

In the TNF-α assay, *A. annua* extract was tested at a range of concentrations from 200 μg/mL to 1 μg/mL. The concentrations of *A. annua* for this dose–response study were selected because preliminary tests (not shown here) indicated that *A. annua* 400 μg/mL completely inhibited TNF-α production by activated neutrophils. Artemisinin was tested at 200 μg/mL and 100 μg/mL. The positive control, chloroquine, was tested at 5 μM (2.58 μg/mL) and 10 μM (5.16 μg/mL). The investigation into PGE_2 production was preliminary, with only three concentrations of *A. annua* tested: 400 μg/mL, 200 μg/mL, and 100 μg/mL. The concentrations selected for this analysis were arbitrary as, to our knowledge, there have been no previous reports of *A. annua* modulating the production of PGE_2 in activated neutrophils. Artemisinin was tested at 400 μg/mL and 200 μg/mL. The positive control, ibuprofen, which is a COX-2 inhibitor, was tested at 400 μg/mL.

Plant extracts and positive controls were dissolved in 100% ethanol. For each sample of plant extract or positive control, 3 μL was added to a 96-well plate. The ethanol was allowed to dry and 20 μL of HBSS was then added to the test wells. A total of 160 μL of the cell suspension was added to each test well. The plate was incubated in a humidified incubator at 37°C in 95% air and 5% carbon dioxide for 20 minutes. Twenty microliters of lipopolysaccharide (LPS; Sigma-Aldrich Co, St Louis, MO, USA) at 100 μg/mL was added to each well (except the unactivated control cells). The plate was incubated at 37°C in 95% air and 5% carbon dioxide. After 24 hours, the plate was centrifuged at 44 *g* for 5 minutes. A 50 μL aliquot from each well was transferred to new 96-well plates for either TNF-α or PGE_2 determination and stored at −20°C until used. Each sample was assayed

in triplicate. As a positive control, triplicate wells with an inhibitor were assayed. As a baseline control, an unsupplemented group was also assessed in triplicate.

Enzyme-linked immunosorbent assay

The enzyme-linked immunosorbent assays (ELISAs) for TNF-α and PGE_2 were performed according to the instruction manual provided by the kit manufacturer (R&D Systems, Inc., Minneapolis, MN, USA) and the absorbance read at 450 nm using a VersaMax™ 96-well plate reader.

Statistical analysis

The percentage standard error of the mean (SEM) for each sample was assessed and extreme outliers were removed if the SEM% was greater than 15%. Preliminary statistical significance was assessed with an independent Student's *t*-test at $\alpha \leq 0.05$ (with and without outliers).

Results

In both assays, the addition of the LPS to the neutrophil cells stimulated them to an inflammatory state.

Inhibition of TNF-α production

For the control cells, the concentration of TNF-α increased 11.89-fold when LPS was included. The positive control, chloroquine, resulted in 23.7% and 42.6% reductions in TNF-α production at 5 μM and 10 μM, respectively.

A. annua extract significantly inhibited TNF-α production by activated neutrophils in a dose-dependent manner (Figure 1). There was complete inhibition by the extract at 200, 100, and 50 μg/mL (all $P \leq 0.0003$). At 25, 10, and 5 μg/mL, *A. annua* extract inhibited TNF-α production by 89% ($P < 0.0001$), 54% ($P = 0.0002$), and 38% ($P = 0.0014$), respectively. At an *A. annua* concentration of 1 μg/mL, TNF-α production was not significantly inhibited (8.8%; $P > 0.05$). Figure 2 shows a dose–response curve of the percentage inhibition of TNF-α production. Artemisinin at 200 μg/mL and 100 μg/mL inhibited TNF-α production by 40.7% and 23.2%, respectively. This is less than that seen with the same concentration of the whole *A. annua* plant extract.

Inhibition of PGE_2

In control cells, the concentration of PGE_2 increased 4.95-fold compared to unactivated cells. Ibuprofen at 400 μg/mL was a very potent inhibitor of COX-2 activity, with a 91% reduction in PGE_2 production. *A. annua* extract significantly inhibited PGE_2 production by activated neutrophils. At concentrations of 400, 200, and 100 μg/mL, *A. annua* extract significantly inhibited PGE_2 production by 87% ($P = 0.0128$), 91% ($P = 0.0017$), and 93% ($P = 0.0114$), respectively. Figure 3 shows the effects of the samples on PGE_2 inhibition by activated neutrophils. As in the TNF-α assay, artemisinin significantly inhibited production of PGE_2, but was not as potent as the whole *A. annua* extract at the same concentration;

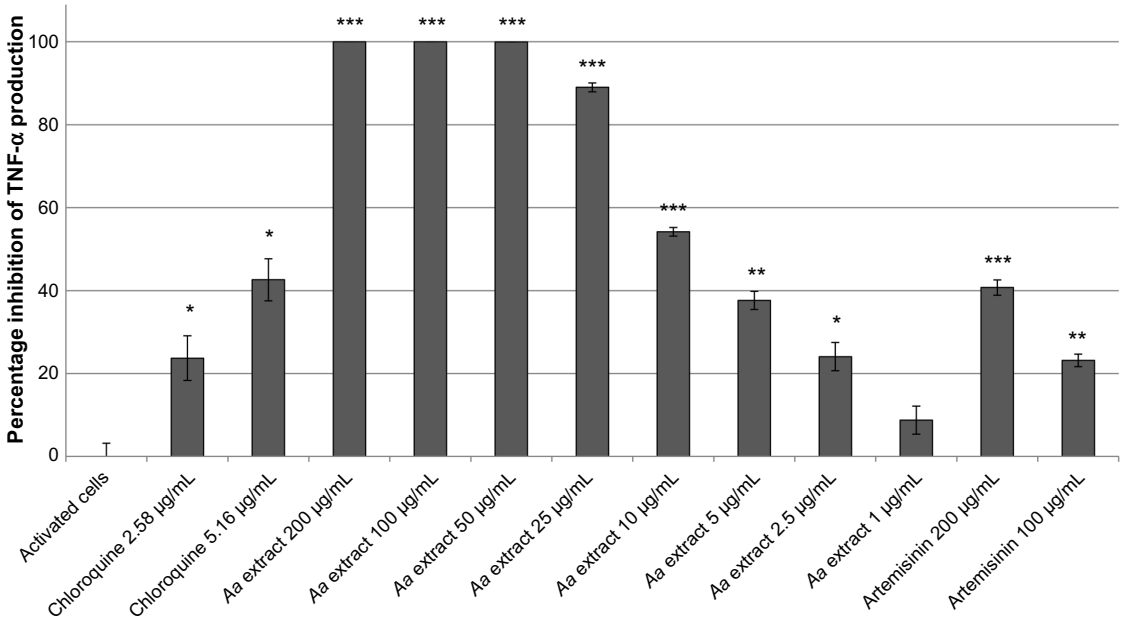

Figure 1 Percentage inhibition (± standard error) of TNF-α production in activated neutrophils.
Notes: *$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$.
Abbreviations: *Aa*, *Artemisia annua*; TNF-α, tumor necrosis factor-alpha.

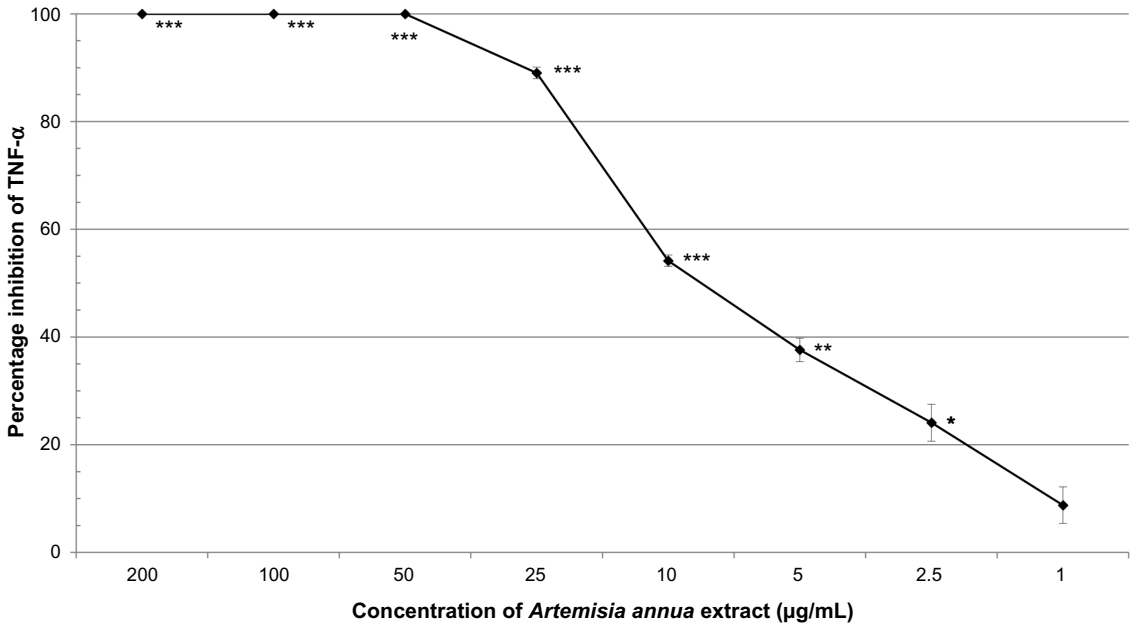

Figure 2 Dose–response of percentage inhibition (± standard error) of TNF-α production in activated neutrophils by *Artemisia annua* extract.
Notes: *$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$.
Abbreviation: TNF-α, tumor necrosis factor-alpha.

artemisinin 400 and 200 µg/mL inhibited PGE_2 production by 65% (P=0.0063) and 57% (P=0.0101), respectively.

Discussion

In this study, the *A. annua* extract was shown to be a potent inhibitor of TNF-α by activated neutrophils with a clear dose–response effect. There was complete inhibition of TNF-α production at concentrations of 50 µg/mL and above. The extract showed statistically significant inhibition of TNF-α production at all concentrations down to 2.5 µg/mL (24% inhibition).

Artemisinin, a well-established bioactive derived from *A. annua,* also inhibited the production of TNF-α by activated neutrophil cells in this study. However, the artemisinin was

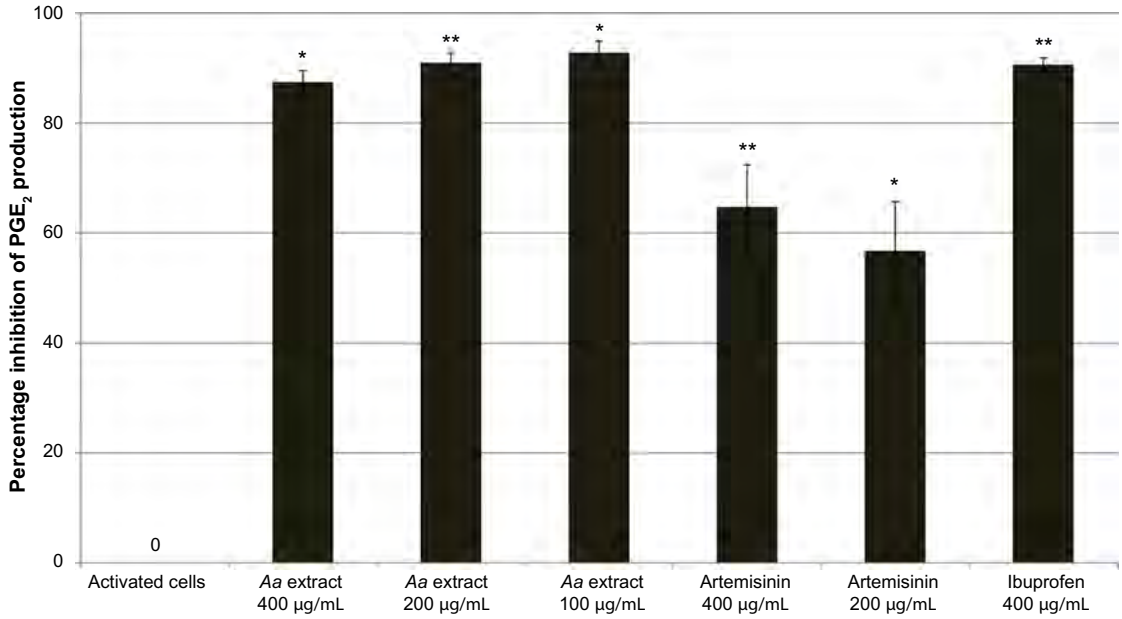

Figure 3 Percentage inhibition (± standard error) of PGE_2 production in activated neutrophils.
Notes: *$P \leq 0.05$; **$P \leq 0.01$.
Abbreviations: *Aa*, *Artemisia annua*; PGE_2, prostaglandin E_2.

not as potent as the whole extract of the plant. The inhibitory effects of 200 μg/mL and 100 μg/mL artemisinin were 40.7% and 23.2%, respectively, while the equivalent concentrations in the whole plant extract were both 100% inhibitory. These results suggest that artemisinin is a strong inhibitor of TNF-α production but that it is not the only antagonist present in the plant extract. It appears likely therefore, that other components of the *A. annua* extract also contribute to its anti-inflammatory bioactivity.

Similar results were seen in the PGE_2 assay, with a significant inhibitory effect displayed for all concentrations of the extract tested. Again, the inhibitory effects of the compound artemisinin were not as potent as the effect of the whole plant extract. This suggests again that there are other bioactive components in the *A. annua* extract, as well as artemisinin, that inhibit the COX-2 activity. This was a preliminary investigation of activity at a small number of concentrations of the plant extract. Inhibition of PGE_2 was similar for all concentrations of *A. annua* extract tested. This implies that 400, 200, and 100 μg/mL *A. annua* extract produced a maximal level of inhibition. Further investigations on dose–response below 100 μg/mL would be needed to find out the potency of *A. annua* extract at inhibiting PGE_2 production.

These results corroborate previous reports suggesting that artemisinin is not the only bioactive compound in *A. annua*.[17,18] A review on traditional *A. annua* use in malaria suggests that the activity of *A. annua* extracts cannot be accounted for by their artemisinin content alone.[17] Another study suggests that artemisinin may act synergistically with flavonoids and polyphenols also present in *A. annua*.[18] It is not known whether either of these classes of compounds are present in the extract tested in this study. Interestingly, in humans, it appears that the bioavailability of artemisinin is enhanced when the entire plant extract is consumed, compared with consumption of pure artemisinin.[19] It is possible that, of the many types of phytochemicals isolated from *A. annua* (sesquiterpenoids, monoterpenes, triterpenoids, flavonoids, coumarins, phenolics, and lipids), several may be responsible for the overall activity and properties of crude plant *A. annua* extracts compared to that of pure artemisinin.[5,20]

While artemisinin may not be responsible for all of the bioactivity in this *A. annua* extract, it is likely that it is one of the most important compounds in the extract. Dihydroartemisinin, a semi-synthetic analog of artemisinin, has been reported to significantly inhibit LPS-induced release of TNF-α, IL-6, and nitric oxide from mouse mononuclear macrophages.[14] Pure artemisinin has been reported to have an anti-inflammatory effect on phorbol myristate acetate–induced THP-1 monocytes.[15]

The extract of *A. annua* used in this study seems to have potent bioactivity. This could partly be due to the physical properties of artemisinin, which is poorly water soluble and is heat labile.[21] The commercial extract used in this study was produced by supercritical extraction of the plant material with carbon dioxide. This type of extraction allows the processing of plant material at low temperatures, limiting thermal degradation, and avoids the use of toxic solvents such as hexane or methane.[22,23]

Studies have previously tested extracts of *A. annua* in vitro, with results reporting a variety of bioactive properties, including protection against oxidative stress,[24] and antioxidant,[25] anthelminthic,[26] and anti-pest[27] properties. However, to our knowledge, this is the first report of in vitro anti-inflammatory properties in this interesting plant.

This study has some limitations. While a dose–response effect was established for TNF-α inhibition in activated neutrophils, the number of concentrations of *A. annua* tested should be increased to establish a dose–response for PGE_2. Similarly, artemisinin was only tested at two concentrations in each assay in this study; further studies would be needed to establish a dose–response for artemisinin. This study was conducted only in activated neutrophils; it would be interesting to establish whether the *A. annua* extract shows similar activity against the production of other pro-inflammatory cytokines in activated macrophages. Toxicity of the plant extract to activated neutrophils was not assessed; further studies should assess any effect of the medicinal plant on cell survival.

Conclusion

In this study in activated neutrophils, an extract of *A. annua* was shown to be a potent inhibitor of TNF-α and a strong inhibitor of PGE_2 production at the concentrations tested. Further studies are needed with this promising plant extract to ascertain whether these in vitro anti-inflammatory effects may translate into in vivo or clinical benefits.

Acknowledgments

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Author contributions

Sheena Hunt designed the study and drafted the manuscript. Mayumi Yoshida and Catherine EJ Davis conducted the

experiments and analyzed the data. Nicholas S Greenhill supervised the study and analyzed the data. Paul F Davis designed the study, analyzed the data, and helped draft the manuscript. All authors revised the manuscript for important intellectual content and read and approved the final manuscript.

Disclosure

This study was funded by Promisia Integrative Ltd. Sheena Hunt is an employee of Promisia Integrative Ltd. The other authors report no conflicts of interest in this work.

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PHARMACEUTICAL SOCIETY
of New Zealand Incorporated

23 August 2019

Jessica Lo
Secretary for the Medicines Classification Committee
Medsafe
Ministry of Health
Wellington

Dear Jess,

Re: Classification of codeine- Information paper for the Medicines Classification Committee

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

The Pharmaceutical Society of New Zealand Inc. (the Society) is the professional association representing over 3,700 pharmacists, from all sectors of pharmacy practice. We provide pharmacists with professional support and representation, training for continuing professional development, and assistance to enable them to deliver to all New Zealanders the best pharmaceutical practice and professional services in relation to medicines. The Society focuses on the important role pharmacists have in medicines management and in the safe and quality use of medicines.

The Society appreciates the work undertaken by the Medsafe team to develop the above codeine information paper, the ongoing discussions at Medicines Classification Committee (MCC) meetings and linkages with the sector.

The Society **supports option A,** to retain the status quo.

The Pharmaceutical Society's view is that the use of combination codeine products over-the-counter is appropriate for adults for acute pain conditions. That the combination of paracetamol and codeine is more effective than either agent alone and is safe and appropriate for the majority of patients.

However, we also acknowledge that improved systems, education support and models of care to identify and manage inadequately managed pain by the health system are required. These would aim to prevent inadequate pain management that may lead to misuse of these products which can progress to dependence and risk of harm.

The widespread availability of shared care systems such as HealthOne and Testsafe would support this, by documenting the supply of medicines bought over-the-counter, for all health care providers approached by a patient.

A clearer understanding of the magnitude of the problem of dependence, misuse and harm is needed, as are the causes of poorly managed pain which lead patients trying to self-manage.

Up-scheduling codeine combination products would not address this and may also lead to greater risk of harm for some patients.

The Society would strongly support a multidisciplinary approach to manage the appropriate use of over-the-counter codeine products that were restricted to pharmacist-only supply and provided an integrated model of care for pain management in primary care.

Additional information is provided below to support these recommendations, using a similar format to the paper prepared by the Medsafe team.

Level 10, Grand Arcade Tower, 16-20 Willis Street, PO Box 11640, Manners Street, Wellington, 6142, New Zealand
TEL 04 802 0030 **FAX** 04 382 9297 **EMAIL** p.society@psnz.org.nz **WEB** www.psnz.org.nz

Classification of codeine in other countries

The Pharmaceutical Society acknowledges the risks reported with over-the-counter combination codeine products in various reports, publications and discussions, most recently regarding the up-scheduling to prescription medicines status in Australia.

The authors of the referenced TGA report used forecasting to determine the impact of up-scheduling codeine in Australia. They are "currently undertaking further analyses of the IQVIA data and will also include comparisons with other data sets (for example, Pharmaceutical Benefits Scheme data) to further understand the impact of up-scheduling on the amounts of codeine dispensed. The TGA will publish the results of these analyses as they are completed".[1] As a result, it is not currently possible to assess the clinical impact of the schedule change until this information has been published.

We would recommend that MCC consider the limitations with the current TGA documentation during their discussions.

Extent of usage in New Zealand

The Medsafe paper uses the pharmaceutical collection to examination the extent of use of codeine in New Zealand. The pharmaceutical collection does show an increase in the number of prescriptions and dispensing's for codeine. However, there are similar increases for prescribed and dispensed morphine and zopiclone.

If the prescribing data set is being used as an indicator of risks attached to codeine and a potential reason for considering a reclassification, then other medicines should also be considered as part of any risk profile around any overdose, abuse and misuse potential.[2]

It is also not possible to extrapolate the prescribing data across to over-the-counter preparations which have been supplied by a pharmacy, as this is not formally captured in these data sets.

Electronic opioid harm monitoring system

The MCC have previously discussed monitoring systems for the sale of codeine, including the Australian model, MedsASSIST and current systems available in New Zealand, including TestSafe and HealthOne.

The Medsafe paper recommends that MCC should not consider an electronic system as a risk mitigation strategy for codeine. However, New Zealand has some systems in place, which are rapidly growing across the country and could be used to record the sale of these products. This includes the use of the pharmacy dispensary programmes. These systems could also integrate with existing patient health records.

With the eMedicines work being driven by the Data and Digital Directorate at the Ministry of Health, suitable risk mitigation strategies and software solutions are either in place or are being introduced by all District Health Boards. The mandatory use of these systems to record the sale of codeine based products could also provide an appropriate monitoring system.

Privacy was raised as a potential concern at previous meetings of the MCC. However, patients requesting inappropriate medication can already be highlighted to other pharmacies under disclosure rule 11(2)(j) of the Health Information Privacy Code 1994.

Genetic polymorphism

CYP2D6 is subject to genetic polymorphism and there are large interethnic differences in the frequencies of the variant 2D6 genes. This results in a small proportion of people (~5-10%) having poor 2D6 enzymatic activity and will fail to produce sufficient active metabolite to elicit an adequate therapeutic response ('poor metabolisers'). While ~1-2% of the population have higher than usual 2D6 expression, and greater amounts of the active metabolite are produced ('ultra-rapid metabolisers'). Approximately 77-92% of people are 'extensive metabolisers' who express 'normal' enzyme activity.[3]

The greater risk of toxicity for ultra-rapid metabolisers taking codeine has gained recognition in a number of reports. However, the context of many of the primary studies needs to be considered, as the risk of opiate intoxication would be **much greater in prescribed doses** of codeine (e.g. 30-60mg every 4 hours maximum 240mg daily, for adult dosing). As one study of the pharmacokinetics of codeine in ultra-rapid metabolisers noted, they did not see any severe adverse effects following a 30mg codeine dose in their rapid metaboliser group.[4]

Clinical outcomes

Many reports have questioned the efficacy of codeine. However, depending on the underlying study design, this may be in part due to poor-metaboliser status, the dose of codeine studied, or perhaps the context of the treatment setting. For instance, the perspective of managing acute moderate-strong pain say in a primary care environment (e.g. dental procedure), differs from more chronic or severe pain settings such as secondary care or patients being managed by specialist pain centres, who have a natural bias towards more complex pain.

The Australian and New Zealand College of Anaesthetists (ANZCA) and Faculty of Pain Medicine (FPM) 2015 publication 'Acute Pain Management: Scientific Evidence' document notes that combination paracetamol 300mg with codeine 30mg provided a greater analgesic effect and longer duration of analgesia than paracetamol alone.[5] While noting a lack of data at combinations with less than 30mg of codeine. The document references a Cochrane Review in noting that:

> *Oral paracetamol combined with codeine is more effective than either medicine alone and shows a dose-response effect (**U**) (**Level I** [Cochrane Review]).* [6]

In the context of acute, short-term pain management, evidence of the efficacy of the combination of paracetamol with codeine is widely available, particularly in oral surgery settings.[7,8] One 2013 review of the use of opioids following oral surgery notes the analgesic response to codeine alone was poor, but was effective when used in combination with paracetamol.[7]

The Medicines Classification Committee may wish to consider the above clinical evidence in addition to the studies discussed in the Medsafe paper.

Benefits and risks of self-selection

Medsafe have stated that "there is good availability of other alternative options than codeine for pain relief". From examination of the relevant data sources non-steroidal anti-inflammatory's and paracetamol would fall into this category. These products do have good availability but do not have the same efficacy as the codeine combination products, which have been noted in the above studies.

Contraindications and precautions

All medicines have specific contraindications and precautions and in practice, appropriate recommendation by the pharmacist would be used for all restricted (pharmacist only) medicines, including codeine preparations.

Medsafe state that "codeine has been the subject of deliberate misuse, and there has been a history of this in New Zealand". A reference to support this statement would be beneficial.

Management of any potential dependence and misuse of medicines is complex. The results of a survey of New Zealand GPs published in 2012 reported approximately two-thirds of GPs had diagnosed at least one patient with a prescription drug misuse problem in the previous 12 months.[9]

The report notes:

> *The action usually taken by the greatest number of GPs once they suspected PDM [prescription drug misuse] was to 'document it' (97.9%) followed closely by 'suggest an alternative drug' (96.7%) and 'refrain from prescribing the drug' (91.9%).*

What we are not made aware of, is the cause behind the misuse or drug seeking behaviour, for instance if poor pain management is creating a dependence or the perception of drug-seeking behaviours. The paper reports GPs would favour support for a range of interventions including training, access to a central database, working with drug and alcohol specialists, more time to attend to each patient, and increased cooperation with pharmacists.[9]

The Pharmaceutical Society would strongly support an integrated approach to the identification and management of patients with potential medication dependence and/or an improved model of care supporting patients with inadequately controlled pain.

Undesirable effects

Medsafe state that "codeine dependency and withdrawal effects are well documented in the scientific literature". A reference would be useful to support this statement.

Overdose and abuse/misuse potential

Codeine is a contributor to patient mortality.[2] However, the incidence of death caused by codeine reduced over the time of the study referenced and only 3.3% of patients died from codeine related incidents.[2] This is significantly lower than the methadone and morphine incidents described in the paper.

It is also not possible to determine if any of the codeine deaths described in the paper were related to prescribed codeine or the medicine being obtained over-the-counter.

According to the Medsafe paper "Death from codeine was considered to be unintentional in 26.4% of patients". This percentage figure is not documented in the primary reference source.

Communal harm

Medsafe state that codeine has been the subject of deliberate misuse and "homebaking" is common practice. The document also states that the formulation of codeine-combined products has been changed to reduce the opportunities for "homebaking". If this is the case, referring to the process of codeine extraction and "homebaking" from the combined medicine may no longer relevant and may not add weight to the case for reclassification.

The FDA has recognised an opioid addiction crisis in the United States, but an epidemic of opioid deaths has not occurred in New Zealand.[2]

The US Centers for Disease Control and Prevention are also starting to see a reduction in provisional drug overdose death counts from opiates.[10]

Integrated benefit-risk statement

Most codeine preparations are currently classified as a restricted medicine, which requires a pharmacist to be involved in the request for treatment and supply. It is not possible for the patient to self-select.

The warnings and precautions are already provided with the provision of the medicine, so this risk has also been mitigated. A reference to support the statement "drug misuse, overdose and abuse leading to hospitalisations, morbidity and even mortality" would be beneficial.

Health equity and wellbeing

The current Government have instructed the health sector to improve population health, which includes strategies to address determinates of health and achieve better health and wellbeing.[11]

The Waitangi Tribunal's report *Hauora: Report on Stage One of the Health Services and Outcomes Kaupapa Inquiry* finds that the Crown has breached the Treaty of Waitangi by failing to design and administer the current primary health care system to actively address persistent Māori health inequities and by failing to give effect to the Treaty's guarantee of tino rangatiratanga.[12]

Pharmacists are the only community health professional who patients can visit without the need for an appointment or payment for initial consultation.

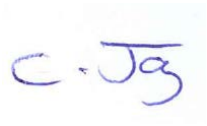
Pharmacists are trained to provide appropriate medicine information and provision of treatment for various conditions, include the management of acute pain.

The Society believes that combination codeine products are appropriate for supply by a pharmacist under a Restricted Medicine classification.

Up-scheduling these products to prescription medicine could increase the burden on General Practitioners, potentially reduce access to appropriate treatments and drive an increase in health inequity.

The Society appreciates the opportunity to provide a response to this submission and we hope our feedback is useful. If you have any questions, please do not hesitate to contact us and we look forward to working with your team as this work progresses.

Yours sincerely,



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The Royal New Zealand
College of General Practitioners
Te Whare Tohu Rata o Aotearoa

26 August 2019

Our Ref: KV19-381

Jessica Lo
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Dear Jessica

"Thank you for giving the Royal New Zealand College of General Practitioners the opportunity to comment on the agenda of the 63rd meeting of the Medicines Classification Committee (MCC) of Medsafe.

General practitioners comprise almost 40 percent of New Zealand's specialist medical workforce and the Royal New Zealand College of General Practitioners is the largest medical college in the country. Our kaupapa is to set and maintain education and quality standards for general practice and support our members to provide competent, equitable care to their patients. We do this to improve health outcomes and reduce health inequities.

Our feedback on the agenda of the 63rd meeting of the Medicines Classification Committee (MCC) of Medsafe is set out below.

Submission

The College would like to comment on agenda item 5.3 The reclassification of codeine.

Background

Currently in New Zealand codeine containing medications are classified in different ways. When in combination with another active ingredient in cough and cold medicines codeine is available on pharmacy shelves and classified as a *pharmacy-only* medicine. When in combination with active ingredients for analgesia codeine is classified as a *restricted* medicine. Other medicines containing codeine are classified as *prescription* medicines.

In December 2016, Australia decided that from 1 February 2018 medicines containing codeine would no longer be available without a prescription. This was contrary to the usual trend of down-scheduling or decreasing the restrictions on access to medicines.

The Australian Therapeutic Goods Administration (TGA) website contains an explanation of the reasons for the change in access to codeine containing medicines. It states;

> "The evidence shows that medicines containing low-dose codeine combined with paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or aspirin, are generally no more effective than other non-codeine medicines.
>
> The use of low-dose codeine-containing medicines is associated with high health risks. Codeine is an opioid drug closely related to morphine and, like morphine, is also derived from opium poppies.

> Codeine, like morphine and other opioids, can cause opioid tolerance, dependence, toxicity and in higher doses, death.
>
> Regular use of medicines containing codeine, for example for chronic pain, has led to some consumers becoming addicted to codeine without realising it. The risks associated with codeine use are too high without oversight from a doctor."[1]

There is an additional concern in New Zealand and in Australia that people addicted to codeine who consume codeine in preparations where it is combined with other medications such as non-steroidal anti-inflammatories or paracetamol are also at risk of the significant adverse effects of these medications.

In accordance with the general principles of Trans-Tasman Scheduling Harmonisation,[2] the MCC reassessed the classification of codeine in New Zealand. At the 59th meeting of the MCC in November 2017 the MCC recommended that:

> "- all codeine in combination medicines, both analgesics and those used for cough and colds, should be reclassified to prescription medicines - medicines containing codeine as the only active ingredient should be reclassified from prescription to restricted medicines; for oral use in adults and children 12 years of age in medicines containing not more than 15 mg per solid dosage unit with a maximum daily dose not exceeding 90 mg of codeine for use as an analgesic and when sold in a pack of not more than three days' supply."[3]

This recommendation aimed to provide access to small amounts of codeine without prescription while decreasing the potential for harm.

However, Medsafe has now referred the recommendation of the 59th MCC meeting back to the MCC. This is because, according to a 2000 policy statement about the scope of the committee, decisions on harmonisation are limited to recommending *whether or not* to harmonise. In addition, the alternative option recommended at the 59th MCC meeting would require time-consuming changes to both the Medicines Regulations and the Misuse of Drugs Regulations.

Accordingly, the MCC will need to decide at its 63rd meeting whether to:

A. Retain the status quo
B. Harmonise with Australia
C. Reclassify as per the recommendation made at the 59th meeting.

We also note that the minutes of the 59th meeting[4] record discussion of a planned real-time recording and monitoring system that would enable pharmacists to identify customers approaching multiple pharmacies requesting codeine.

The College position

On balance the College supports option B: to harmonise with Australia.

This would mean that all medicines containing codeine would be classified as prescription medicines. This more restrictive classification of codeine would likely assist in decreasing the use of codeine in New

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[1] https://www.tga.gov.au/codeine-info-hub
[2] https://www.medsafe.govt.nz/profs/class/harmon.asp
[3] https://medsafe.govt.nz/profs/class/Agendas/Agen63/MCC63_53a_Reclassificationofcodeine.pdf
[4] https://www.medsafe.govt.nz/profs/class/Minutes/2016-2020/mccMin7Nov2017.htm

Zealand as has been the case in Australia.[5] It can be expected that there will also be an associated decrease in codeine related harm in New Zealand.

The College acknowledges that harmonisation will remove access to non-prescription supply of codeine in some situations where short term use may be appropriate, e.g. toothache.

The College would give consideration to supporting the down-scheduling of low-dose, short-term codeine if:

a. There was an effective system of mandatory real time monitoring of restricted medicines such as codeine, and
b. The MCC consulted on such a proposal in the future.

We hope you find our submission helpful. Should you require any further information or clarification please contact the College's policy team at policy@rnzcgp.org.nz.

Yours sincerely,

Karen Vaughan
Head of Stakeholder Relations

[5] https://www.tga.gov.au/media-release/significant-decrease-amount-codeine-supplied-australians