PHARMACEUTICAL SOCIETY
of New Zealand Incorporated

23 August 2018

Medicines Classification Committee Secretary
Medsafe
PO Box 5013
Wellington 6145
via email: committees@moh.govt.nz

Dear Jessica,

MEDICINES CLASSIFICATION COMMITTEE (MCC)
COMMENTS TO THE 61st MEETING AGENDA Friday 2nd November 2018

Thank you for the opportunity to submit comments on the Agenda for the 61st meeting of the Medicines Classification Committee.

The Pharmaceutical Society of New Zealand Inc. (the Society) is the professional association representing over 3,000 pharmacists, from all sectors of pharmacy practice. We provide to pharmacists 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.

Regarding the agenda items for the above meeting of the Medicines Classification Committee, The Pharmaceutical Society would like to note the following comments for consideration:

5.1.1 Reclassification of modified release paracetamol from pharmacy-only to a restricted medicine.

The Society supports the original recommendation made by the Medicines Classification Committee to reclassify modified release paracetamol to a restricted medicine.
This would ensure any potential overdose by patients taking the wrong number or frequency of 665mg tablets, compared to the standard 500mg tablet is significantly reduced.
The management of paracetamol overdose is important to consider when patients accidentally consume too much paracetamol. New Zealand has robust guidance around the management of paracetamol overdose which will ensure appropriate treatment. However, reviewing and reducing the potential risk of an overdose occurring is also important. Reclassifying modified release paracetamol to a restricted medicine will help with managing this risk.

5.3 Referred submission from the 60th meeting: Melatonin Medicine reclassification – proposed process when considering the reclassification of prescription medicine to restricted medicine

The Society appreciates the detailed information provided by the applicant but does not support the proposal to return oral melatonin in doses of 3mg or less to an over the counter use or food supplement. The Society also does not support the applicant's proposal to request a pharmacist to supply an unapproved medicine as a restricted medicine.
The Society understands the applicants request for changing of the legislation to supports their submission but does not support the recommendation because it may set a precedent for other products that could be classed a dietary supplements overseas but non approved medicines in New Zealand.

6.1 Melatonin prolonged release 2mg tablets- proposed reclassification from prescription medicine to prescription except when classification (Circadin, Aspen Pharmacare and Natalie Gauld Ltd)

The Society supports this application, if the Committee are satisfied that the applicants have addressed the committees concerns raised at the 49th Medicines Classification Committee meeting (17th June 2013) and the applicants can demonstrate that the potential pharmacist assessment tools are robust, referenced, outcome and evidence based.

6.2 Dextromethorphan, Opium tincture, squill oxymel and phocodine- proposed reclassification from general sale and pharmacy only medicines to restricted medicines (Medsafe)

The Society understands the reasoning behind Medsafe's application to the Medicines Classification Committee but does not support the reclassification of Dextromethorphan and Phocodine linctus.

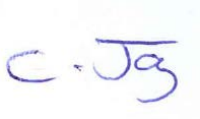
Medsafe have produce a comprehensive review of Dextromethorphan from an international perspective but the evidence to support a reclassification in New Zealand is small. Also, some of the products used in other jurisdictions are not available in New Zealand.

Medsafe's application and evidence to consider a rescheduling Phocodine is really small. The final sentence of their discussion paper also supports the status quo "The effects of pholcodine are uncertain, but the additive potential is considered to be low."

The Society supports Medsafe's application to the Medicines Classification committee to reclassify Gees linctus (Opium tincture, squill oxymel) due to the significant amount of alcohol and small amount of anhydrous morphine.

Thank you for consideration of this submission. I would be happy to discuss any aspect of this submission further, if required.

Yours sincerely,



Chris Jay
Manager Practice and Policy
p: 04 802 0036
e: c.jay@psnz.org.nz

Dr Stewart Jessamine

133 Molesworth Street
Thorndon
Wellington 6011

16th March 2018

Dear Stewart

We are writing to you to notify you of two incidents relating to Robitussin dry cough capsules, a General Sale medicine which we understand is widely available through New Zealand retailers.

We seek your advice on two matters. First, are you are aware of other incidents of this nature involving this product and second, can you provide us any guidance given the inherent risk? We assume there are wider public health issues to consider, including an across industry response.

The two incidents are as follows: On 10th January a Christchurch Countdown store Manager took a call from a concerned customer whose son had been able to purchase Robitussin dry cough capsules on a regular basis and had enough tablets to give himself a “high”. The son advised his parents that a lot of his friends are now doing this as it’s a cheap way to get a high from a drug.

On Friday 9th March our customer contact centre took a call from a concerned Auckland father whose fifteen year old daughter had consumed twenty capsules to achieve a high and ultimately ended up in hospital. He referred to it as "a popular recreational drug for teenagers" and was purchased by her daughter and her friends knowingly to be misused.

In both cases we have notified the manufacturer, Pfizer. As you’d expect, as responsible retailer we want to do the right thing. We’d appreciate any guidance you can provide on how we could respond to the concerns as outlined.

Yours sincerely

Jeremy Armes

Countdown Business Manager for Pharmacy & Healthcare

To: committees@moh.govt.nz,
Date: 01/09/2018 05:24 p.m.
Subject: AGENDA FOR THE 61ST MEETING OF THE MEDICINES CLASSIFICATION COMMITTEE TO BE HELD IN WELLINGTON ON FRIDAY 2 NOVEMBER 2018 AT 9:30 AM

Hi, I would like to support the proposal from Medsafe for the reclassification of cough medicines containing the active ingredients dextromethorphan, from general sale and pharmacy-only medicines to restricted medicines.

I am the farther of a 16 year old.

Earlier this year my daughter purchased Robitussin dry cough capsules from a supermarket and consumed the whole packet in the hope of obtaining a “small buzz”.

She soon experienced a racing heart, confusion, and a very strong out of body feeling. Luckily for us, her friends brought her home and we took her to AEE (Auckland) where we stayed for four hours under observation.

No lasting effects.

My daughter was reckless in consuming something when she didn’t understand what might be the risks or consequences of her actions

However it seems wrong to be able to buy, without any control, a drug that can have such an adverse effect.

So I support at least a ‘pharmacy only’ classification for the relevant types of cough suppressants.

Regards

[redacted]
Westmere[attachment "MCC_Public_Consultation_Cover_Sheet.docx" deleted by Jessica Lo/MOH]

<MCC_Public_Consultation_Cover_Sheet.docx>

From: Nick Paterson <Nick@drugfreesport.org.nz>
To: '"committees@moh.govt.nz"' <committees@moh.govt.nz>,
Cc: 'Trish Bradley' <Trish.Bradley@sportnz.org.nz>
Date: 31/08/2018 04:23 p.m.
Subject: RE: Invitation to provide feedback on the agenda for the 61st meeting of the Medicines Classification Committee

Good afternoon

Further to your email to Sport NZ, we have made the following brief comments on your agenda for the 61st meeting:

DFSNZ support recommendations to classify these substances so as to regulate their availability.

Stenabolic SR9009 and other synthetic REV-ERB agonists
SR9009 is prohibited under section S4.5 Hormone and Metabolic Modulators of the 2018 WADA Prohibited List. Experiments in mice identify Rev-erb-α as a physiological regulator of muscle mitochondrial content and oxidative function[1], thus highlighting it's potential to enhance sporting performance.

1. Woldt, E. et al. 2013 Rev-erb-α modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy. Nat Med 19(8): 1039-1046

Ibutamoren
Ibutamoren also known as MK-677, MK-0677, Oratrope is prohibited under Section S2.2.3 Peptide Hormones, Growth Factors, Related Substances and Mimetics of the 2018 WADA Prohibited List. It is an endogenous ligand for the Growth Hormone secretagogue receptor shown to elevate growth hormone in dogs[2]. GH secretagogues are used by athletes to enhance performance as they are purported to aid recovery from injury and influence metabolism to increase lean muscle mass and decrease body fat.

2. Patchett, A.A., Nargund, R.P., Tata, J.R., et al. Design and biological activities of L-163,191 (MK-0677): A potent, orally active growth hormone secretagogue. Proceedings of the National Academy of Sciences of the United States of America 92(15), 7001-7005 (1995).

If you ned any further information, please let me know.
Kind regards
Nick

Nick Paterson
Chief Executive

Paediatric Society New Zealand

NZCYCN New Zealand Child & Youth Clinical Network

11 September 2018

New Zealand Medicines and Medical Devices Safety Authority
Medicines Classification Committee
c/o MCC Secretary at committees@moh.govt.nz

I am writing on behalf of the Paediatric Sleep Medicine Clinical Network, in regard to Agenda item 5.3 for the upcoming 61st meeting of the Medicines Classification Committee. The item relates to Melatonin for oral use in doses of 3 mg or less as a restricted medicine.

In New Zealand Melatonin is currently only registered for use in patients >55 years with primary insomnia. It is available on Special Authority for children under the age of 18 years with neurodevelopmental disorders. We are concerned that allowing over-the-counter purchase of melatonin will increase the use of melatonin in children and young people in situations when it is inappropriate or without due regard to safety.

Melatonin is frequently perceived as a safe "natural hormone" rather than a drug. Parents surfing the internet are likely to get conflicting information on its safety and side effects. Difficulty falling asleep and/or maintaining sleep may be due to a variety of sleep issues or disorders. The suggested approach to a child with a sleep problems is to undertake a thorough sleep and medical history, combined with a careful physical examination. First line treatment for children with difficulty sleeping would be attention to good sleep habits and behavioural sleep measures. Melatonin may be used second line and "off label" for children with protracted difficulty sleeping, particularly if they have underlying neurodevelopmental problems.

We are concerned that over the counter availability of Melatonin would lead to its use prior to adequate evaluation of the many causes of difficulty falling asleep and/ or maintaining sleep. Melatonin should only be considered following adequate trial of appropriately implemented behavioural sleep measures and attention to good sleep hygiene[1]. "Although the institution of positive sleep-hygiene measures by themselves may not be sufficient to adequately treat sleep problems in children….other interventions are unlikely to be successful if poor sleep habits are not recognized and addressed" Jan et al[2]. Other underlying medical conditions that may affect sleep (eg pain, sleep disordered breathing, gastro-oesophageal reflux, etc) should be diagnosed and treated, and concomitant medication use reviewed, before any trial of melatonin. We have previously suggested that melatonin only be prescribed in children after discussion with a specialist paediatrician. This allows for dialogue around a thorough sleep and medical history, diagnosis and management of other sleep issues.

We strongly support follow-up and review of prescriptions 6-12 monthly due to the lack of studies on the potential side effects of prolonged usage in children. Ideally Melatonin should be discontinued for 1 week every 12 months after a normal sleep cycle is established to assess ongoing need for therapy.

Mean daily melatonin production in adults is 28.8mcg/day (20-60mcg/day)[3], so all suggested exogenous treatment regimens are vastly in excess of physiological levels. In some patients who are slow metabolisers of melatonin the initial response diminishes within a few weeks, as melatonin accumulates and the circadian melatonin rhythm is lost[4,5]. This is thought to effect 12-14% of the population, but may be more common in children with neurodevelopmental disabilities[4]. Without appropriate advice and surveillance, this can lead to escalating doses (rather than to appropriate dose reduction).

In general, melatonin appears to be well tolerated in children, including with longer-term use[6]. Potential side effects include headache, nausea, dizziness, increased nocturnal enuresis, and sedation[1,4-8]. These tend to be mild and self-limiting. However the safety of very long term use is

unknown and concerns remain. Animal research shows that melatonin has effects on pubertal development and seasonal reproduction in a variety of non-human mammals[3,7]. While adverse effects on puberty and reproductive function in humans have not been shown[6], this has not been rigorously studied in large randomized controlled trials.

Finally, chronic melatonin administration causes activation of the immune system[2], and should be avoided in children with autoimmune or lymphoproliferative disorders, and those on immunosuppressive medication[10]. Weak conflicting evidence suggests that melatonin may either increase or decrease the seizure threshold in epilepsy, and caution is recommended[3,4,7,10].

In summary we advocate for melatonin prescription in children only after thorough assessment and ongoing surveillance by a health professional.

Kind regards

Dr Sarah Currie
Paediatrician
NZ Paediatric Sleep Medicine Clinical Network

NZ Paediatric Sleep Medicine Clinical Network Clinical Reference Group Members:

- Elizabeth Edwards (Chair), Paediatrician,Respiratory & Sleep Medicine, Starship Children's Hospital
- Rachel Sayers (Facilitator), Assistant Research Fellow, Department of Women's and Children's Health, University of Otago and Lecturer, School of Nursing, Otago Polytechnic
- Alex Bartle, Director of the Sleep Well Clinic
- Angela Campbell, Manager, Well Sleep Centre, University of Otago
- Sarah Currie, General Paediatrician, Hawkes Bay DHB
- Dawn Elder (Prof) HOD Department of Paediatrics & Child Health, University of Otago Wellington; Paediatric Sleep Physician
- Marie-Francoise Jean-Louis, Paediatric Otolaryngologist, Health Waikato
- Barbara Galland, Research Assoc Prof, University of Otago
- Nikki Mills Paediatric Otolaryngologist, Auckland DHB
- Karen Munro, General Paediatrician Waitemata DHB
- Philip Pattemore, Paediatrician Respiratory/General & Associate Professor of Paediatrics, University of Otago
- Barry Taylor (Prof), Dean, Otago University
- Jacob Twiss, Paediatrician, Respiratory & Sleep Medicine, Auckland DHB

References

1. Owens JA, Babcock D, Blumer J, Chervin R, Ferber R, Goetting M, et al. The use of pharmacotherapy in the treatment of pediatric insomnia in primary care: rational approaches. A consensus meeting summary. Journal of Clinical Sleep Medicine. 2005; 1(1): 49-59

2. Jan JE, Owens JA, Weiss MD, Johnson KP, Wasdell MB, Freeman RD, Ipsiroglu OS. Sleep hygiene for children with neurodevelopmental disabilities. Pediatrics. 2008 Dec;122(6):1343-50

3. Kennaway DJ. Potential safety issues in the use of the hormone melatonin in paediatrics. Journal of Paediatrics and Child Health. 2015; 51: 584-589

4. Bruni O, Alonso-Alconada D, Besag F, Biran V, Braam W, Cortese S, et al. Current role of melatonin in pediatric neurology: clinical recommendations. Eur J Paediatr Neurol. 2015 Mar;19(2):122-33

5. Rossignol D, Frye R. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. Dev Med Child Neurol. 2011 Sep;53(9):783-92

6. Andersen L, Gogenur I, Rosenberg J, Reiter R. The safety of melatonin in humans. Clin Drug Investig. 2016; 36:169-175

7. Stores G. Medication for sleep-wake disorders. Arch dis Child 2003; 88: 899-903

8. Melatonin for sleep problems in children with neurodevelopmental disorders. [No authors listed] Drug Ther Bull. 2015 Oct;53(10):117-20

9. Macchi M, Bruce J. Human pineal physiology and functional significance of melatonin. Frontiers in Neuroendocrinology 2004: 25: 177-195

10. Janjua I, Goldman R. Sleep-related melatonin use in healthy children. Canadian Family Physician 2016; 62:315-317

New Zealand Medical Association
Te Hauora mō ngā Iwi Katoa

31 August 2018

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

Agenda for the 61st 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 three items on the agenda for the 61st meeting scheduled for 2 November 2018.

Items 5.3 and 6.1 (reclassification of melatonin)
We note that the 61st meeting of the MCC will consider two separate agenda items regarding the reclassification of melatonin. Item 5.3 relates to the proposed reclassification of oral melatonin in doses of 3mg or less from prescription medicine to restricted medicine. Item 6.1 relates to the proposed reclassification from prescription medicine to prescription except when provided at a strength of 2mg prolonged release to people who meet clinical and eligibility criteria when sold by a pharmacist who has completed an approved training programme.

We are supportive of a regulatory framework that supports better access to melatonin (including taking into account cost to patients) while ensuring appropriate use (particular concerns relate to the long-term use of melatonin and of parents medicating children) and safeguarding standards of safety, efficacy and quality (including good manufacturing process).

A reclassification from prescription medicine to prescription except when provided at a strength of 2mg prolonged release to people who meet clinical and eligibility criteria when sold by a pharmacist who has completed an approved training programme should address concerns about inappropriate use and may also improve access for some patients. However, the cost of a pharmacist consultation is likely to represent a significant barrier for many people.

While a reclassification of melatonin from prescription to restricted medicine could be expected to improve access and cost (no pharmacist / GP consultation fee), it could widen inappropriate use even though it provides for some monitoring of patterns of purchase. Furthermore, our understanding is that if a medicine is changed to restricted (pharmacist-only) status, it would potentially allow importation of unregulated melatonin from overseas with all the attendant concerns about poor quality and lack of oversight.

We recommend that the committee balance all these factors when determining which regulatory option is best for melatonin.

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Item 6.2 Dextromethorphan, opium tincture, squill oxymel and pholcodine reclassification
We support the reclassification of the above opioid (and opioid-like) cough medicines from general sale and pharmacy-only medicines to restricted medicines. This measure harmonises the regulation of opioid derivatives and is an important step towards reducing the well-known potential for abuse of these medicines.

We hope our feedback is helpful.

Yours sincerely

Dr Kate Baddock
NZMA Chair

Further Comments on my Submission on Melatonin
and on the Aspen Circadin Submission
Chris King 13th September 2018

In the light of the referral of my submission[1] back to the Medicines Classification Committee, I have several comments on the question of allowing mail importation of melatonin-containing food supplements for personal use, as outlined in (b) of the submission. As these were notified in the original submission, they need to be addressed at the forthcoming meeting.

The Classification Committee has indicated that they still consider melatonin to be a medicine and thus subject to the Medicines Act's provisions. I have considered this in detail since attending the last meeting and believe that this position is fraught with contradictions and urgently needs redressing, both because of manifest inconsistencies in this classification's application and in terms of the impediments placed by section 29 of the Medicines Act, which create a potentially impossible situation for rational treatment of melatonin as a medicine.

1. The Status of Prescription Melatonin in New Zealand is Contradictory.

On the one hand, melatonin is treated by the Committee as a medicine, for reasons which are scientifically unconvincing, and on the other hand it is not accepted as a pharmaceutical and is thus subjected to the provisions of section 29. This means it may not be able to be pharmacist-only or be subsidized and results in an untenable situation, where those people prescribed melatonin by a doctor have to pay excessive fees for what would only be a fraction of the cost by mail order and even when they do purchase it by prescription in NZ, it is not a medicine at all but rather a food additive prepared in the US under Federal Good Manufacturing Practice (GMP), but not as a drug with FDA evaluation.

The commonly prescribed brand available in NZ from Worldwide Labs on prescription states clearly and unambiguously on the label (see illustration in section 7) that it is a food supplement, not a medicine: "**Dietary supplement** – A safe effective natural sleep aid". The label specifically notes that: "These statements have not been evaluated by the FDA. **This product is not intended to diagnose, treat, prevent or cure any disease**". For the rest of the commentary I will refer to this as "natural melatonin".

The committee is thus patently in the process of promoting a manifest contradiction, claiming melatonin is a medicine and then effectively requiring doctors to prescribe a food supplement that states in plain English that it is NOT a medicine, which the recipient should rightly be empowered to make their own decision about.

To insist something is a medicine and then provide for it as a food additive is manifestly misleading, legally, scientifically and factually – a fallacy whose only valid course of action in response is declassifying it as it was in NZ until April 1996 when the Committee "urgently" made it a prescription drug, claiming "it is a hormone and that at the time there was insufficient data available regarding its effects and safety profile" presumably in response to claims it was an effective sleep remedy.

The underlying reason it is a food additive, even on prescription, is that the in the huge US market it is classified as a dietary supplement, and so there is no incentive for drug manufacturers to research its safety exhaustively according to the Committee's exacting

[1] http://medsafe.govt.nz/profs/class/Agendas/Agen61/53Melatonin.pdf

standards and market it to the tiny New Zealand market on any other basis. It has thus gained effective status as a dietary supplement, been found safe, and needs to be treated as such.

To classify it as a medicine results in impossible demands to verify that it is safe because the Committee quotes rigorous standards of research into side effects which can be financially sustained only by a pharmaceutical industry marketing a costly or subsidized product, when the key international market in the US treats it as a safe dietary supplement by standards of continued use without harm by millions in the US, as the fourth most widely used supplement in a survey by Centers of Disease Control cited in my submission. The pharmaceutical research is thus never going to be forthcoming, resulting in a procedural impasse caused directly by the Committee insisting on classifying it as a medicine when it is used by healthy people, to help regulate the consequences of a technological urban lifestyle involving let-lag, shift work and evening blue lighting, as well as for circadian sleep disorders.

2. Status of Melatonin under Section 29 stipulates allowing for Personal Mail-order

Giving melatonin Section 29 Status by claiming it is a medicine but knowing it is not a pharmaceutical appears to put the Committee in the position of effectively paralyzing it from being provided as a pharmacist-only restricted medicine, because this appears to be possible only for genuine medical pharmaceuticals, when melatonin as prescribed is not a medicine.

This mandates that the Committee takes a constructive lead in formulating a rational solution. The Medicines Act is in the process of a review, but the website link[2] sent to me by Jessica Lo states that the last update prior to the change of government was December 2017 and all the linked reports appear to date back even earlier to 2016, so there is no basis for any action on this front over this issue in real time.

This issue could and should readily be solved, simply by Medsafe making an internal directive not to seize and hold shipments of melatonin-containing dietary additives imported from verified US herbal suppliers by mail order for personal use, as my original submission requested, with provided evidence of this in other countries such as Australia and Canada.

This would also serve to save the postal service scrutiny and seizure costs, having to survey all products incoming from the US from any legitimate herbal supplier, on the basis it might involve melatonin-containing food additives.

There is another reason why this is really essential. Because the US market treats melatonin as a food supplement, there are a spectrum of products containing both permitted herbal and other natural supplements and varying amounts of melatonin. There is no rational way to determine which should be treated as medicines and which should be allowed in as dietary supplements. In fact they are ALL food supplements! Despite the attempts to block innocent formulations such as “Chocolate Sleep Bytes” containing natural chocolate and melatonin, there are diverse other products Medsafe doesn’t seize, creating an inconsistent regime in which some products are still available by mail order, which leaves both the mail order purchaser and Medsafe in an ambiguous and needlessly costly situation.

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[2] https://www.health.govt.nz/our-work/regulation-health-and-disability-system/therapeutic-products-regulatory-regime

3. Circadin, Children and Pharmac Subsidies

While we support the ability of Circadin to be classified as a pharmacist-only product rather than a prescription drug as per my original submission's intent, Circadin is a delayed release formulation and much more costly even than prescribed unsubsidized natural melatonin.

This has already resulted in paradoxical situations emerging. While the Committee rejected Circadin's previous application for non-prescription status on the inflated claim that too little research had been done on the delayed release formulation and over concern about giving it to children, we find that Pharmac has seen fit, based on the medical evidence, to proactively subsidize prescription melatonin for sleep disorders in children under 18 (despite this use not being registered with Medsafe) but because of its orphan status, they do not subsidize natural melatonin, so instruct parents wishing to give it in a drink to crush Circadin tablets and give them at bedtime[3] as natural normal release melatonin (see Appendix):

Who is melatonin funded for? Melatonin (brand name 'Circadin') will be funded from 1 July 2017 for children and young people up to the age of 18 years who have neurodevelopment disorders that make it difficult to sleep.
More information on Circadin use in children The Circadin brand of melatonin is the only brand of melatonin registered in New Zealand. It is registered for people aged 55 years or over. This means that its use in children is "off-label" (a use not registered with Medsafe) and needs to be discussed with a doctor.
What about crushing Circadin tablets? The BPACnz article advises that for children who are unable to swallow tablets the modified-release tablets can be crushed and mixed with a drink. This means the tablets would no longer be modified release and should be given immediately before bed time. Crushing the Circadin tablets is not recommended by the supplier and would need to be discussed with your doctor or pharmacist first. Last updated: 26 June 2018.

This is manifest evidence that regulation in NZ is in conflict of purpose and contradiction.

4. Avoiding unfair Market Competition against Natural Melatonin

In the light of my submission, I was informed by Natalie Gauld, in a courtesy call, that the marketers of Circadin in NZ - Aspen Pharma and Natalie Gauld Ltd.[4] may seek to have their product given the same status as sildenafil and that it is the only product that can be made so, because of Section 29. This initiative is confirmed in their accompanying submission:

This application is seeking the reclassification of melatonin in prolonged release 2 mg oral dose form to Prescription Medicine except when supplied in approved manufacturer's packs by a pharmacist who has undergone specified training on insomnia.

Aspen is marketing a proprietary medicine for profitable sale. The problem is that they actively seek to retain Circadin as prescription-only except specifically as a medicine for insomnia requiring special pharmacist training, when the actual substance they are selling is simply a slow-release form of natural melatonin. Actively seeking its status as a medicine would also effectively secure them a monopoly over non-prescription marketing.

Our submission is for natural melatonin 3 mg to simply become a pharmacist restricted natural substance not requiring a prescription and be allowed to be imported as a dietary supplement by mail order for personal use. The two submissions are not inconsistent, but the

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[3] https://www.pharmac.govt.nz/medicines/my-medicine-has-changed/melatonin/
[4] http://medsafe.govt.nz/profs/class/Agendas/Agen61/61MelatoninSubmission.pdf

consistency depends on both submissions being successful. If only Aspen is successful, NZ will enter a regime where non-prescription use is exclusively granted to a single proprietary pharma, a contradiction in terms for a natural substance that we all secrete nightly.

In the context of sildenafil, there is no significant competition with dietary supplement products, although these also abound, because there is no precise natural form of sildenafil and there are no significant pricing conflicts, since Viagra is now out of patent limits in NZ and is similarly priced to generics.

Furthermore sildenafil is not a natural substance, but a research designer drug that has profound effects on both erectile and other functions that is clearly a medicine requiring some expert pharmacist training and subject evaluation, by contrast with melatonin, which is a natural substance whose side effects are minimal to non-existent. We therefore see the status of melatonin as a non-prescription pharmacy restricted product as fully appropriate.

Aspen is fully entitled to describe and market their product as a proprietary medicine for insomnia but this doesn't mean that natural melatonin itself is a medicine, or has to be legally defined to be a medicine, as US legislation shows. Melatonin is clearly a natural substance produced by virtually all organisms as a primary antioxidant and used as a circadian primer in organisms from single-celled *Tetrahymena* to *Homo sapiens*, as our submission detailed.

We thus support the Aspen submission concerning Circadin, with strong reservations. On the positive side, this is a good response to the Committee's reluctance historically to release Circadin from prescription–only status presented again now in the light of our own submission to the previous meeting. On the negative side, we see this as a covert means to both give the proprietary version greater marketability and corner the non-prescription market entirely due to the orphan Section 29 status of natural melatonin and the claim by Aspen that Circadin is a medicine requiring as strict a regime as sildenafil.

We see targeting Circadin as the only non-prescription option as a highly undesirable development, because of the severe cost to the user, whether a patient or a healthy person seeking circadian stablilization due to lifestyle pressures. It is very important to avoid the non-prescription market becoming monopolized by an expensive proprietary product that is simply melatonin in a graduated release coating, which should in real market terms cost no more than twice the price of the mail-order dietary supplement.

The Committee thus urgently needs to constructively address part (b) of our original submission and provide a safety valve for those people who do not want a delayed release formulation and do not want to pay the excessive cost for buying Circadin tablets and crushing them, or having to get a doctor's prescription for the NZ food supplement version.

The correct safety valve, whether or not the Committee considers itself to be powerless about Section 29, is to allow the importation of melatonin as a natural supplement for personal use as in several other countries with similar medicine regimes noted in my original submission. To sit on one's hands about this is a declaration of insufficiency to the general public.

5. Ethical Conclusion

The claim that melatonin is a medicine and therefore must be controlled by the Medicines Act and subjected to research pharmaceutical standards that are appropriate only for new designer drugs, or remain locked in Section 29 as an orphan de-facto dietary supplement is

fundamentally invalid. Melatonin is used worldwide by healthy people to regulate disruptions to circadian rhythms caused by the manifold impacts of modern technological civilization. The Committee seriously erred in 1996 by urgently classifying it on the false basis that it was a "hormone" and citing unspecified claims that too little research had gone into its safety.

Melatonin is an ambiphilic transmitter targeting neuronal and other cellular membrane receptors and is not a hormone in the sense that classic steroid hormones can pass through the membrane and interact directly with nuclear proteins and have significant side effects such as droid rage. Caffeine could likewise be classed as a "hormone" because it acts upon the adenosine receptor, but the Committee recognizes that classifying caffeine as a medicine is unconscionable and unachievable.

Yet the uses of melatonin and caffeine are very similar. Both are used by healthy people to mediate the physiological and mental impacts and attritions of modern society. While caffeine has known side effects and risks e.g. of hypertension, the side effects of melatonin are few to non-existent. Neither is there any established evidence that regular use of melatonin results in tolerance, craving, withdrawal effects or long term health issues. Many vitamin supplements that are freely available in NZ including vitamins A and E have been demonstrated to cause marked increases in cancer rates, yet the Committee takes no action about these.

Maintaining tight control on the use of melatonin has all manner of undesirable and potentially lethal social consequences, because it results in increased unnecessary use of benzodiazepines, Z-drugs, alcohol and black market sedatives such as GHB, all of which have major tolerance, withdrawal rebound effects, increases in cancer and dementia rates, overdoses and lowered life expectancy.

It is morally repugnant and ethically indefensible for the Committee to continue to classify melatonin as a prescription medicine without due convincing evidence to justify it, seemingly on the basis that continuing control will be the safest course of action, because no risks will occur to the Committee by making a status quo non-decision or merely allowing Circadin on the basis of the Aspen submission.. I thus urge the Committee to demonstrate it is capable of acting in the public interest and release melatonin from the ill-considered 1996 decision and give all forms non-prescription pharmacist restricted medicine status.

6. A Personal Update

I have been taking 1.5 mg of natural melatonin nightly for around 5 years. I have noticed no reduction in its effectiveness, experienced no side effects, and it has enabled me to stop using sedatives almost entirely after two severe bouts of sleep onset insomnia that rapidly crippled my health. I neither need nor want a 2 mg delayed release medicinal formulation.

This year melatonin supplementation enabled me to get through a horrific family health crisis without ongoing insomnia when my adult son was grievously attacked by gang affiliates after they clipped his vehicle on a gang ride and he got out to make sure they were okay. He was knocked to the pavement with a king punch and sustained multiple skull fractures and a significant traumatic brain injury with a month to go to complete his PhD in neuroscience. Through the months of recovery that have followed I have continued to manage to get sleep, requiring only two half zopiclone tablets in the entire four and a half month period, thanks to the 1.5 mg melatonin. I do not consider myself a patient with a medical condition and find it unacceptable to be treated as such by the Classification Committee and to have to repeatedly go back to my medical practitioner to be allowed to continue to use what I was originally able

to mail order at low cost as a dietary supplement, until Medsafe began making lists of every herbal product they could find containing melatonin and seizing them. This mindless misadventure in the name of public health regulation needs urgently to be revoked.

7. Key Price Comparisons

1. US iHerb mail order 90 3 mg (3 months supply) $US 8.13 ~ $NZ 12.50 (inc shipping)

21st Century, Melatonin, 3 mg, 90 Tablets
By 21st Century
396 Reviews | Questions
In Stock
Potency: 3 mg
3 mg NZ$5.79
5 mg
Package Quantity: Count
Count NZ$5.79
200 Count NZ$9.27
120 Count

Order Summary
Subtotal: $3.37
Loyalty Credit $0.00
Shipping: $4.76
Rewards Credit: $0.00
Order Total: $8.13

2. NZ Circadin 90NZ $135 - $178 ($45-$59 for 30) depending on the pharmacy, but this is 2 mg so the equivalent price to the above for the same melatonin content is $NZ 202.50 - $267 as a restricted medicine and with a doctors/prescription fee of $20 - $50 comes to $222.50 - $317 for prescribed medication.

3. Prescription melatonin World Scientific Labs: $50 for an initial prescription with a doctors visit and $20 for a repeat plus $52 - $90 for 90 3 mg tablets – all in all a price of $70 - $140.

Appendix

Melatonin (Pharmac)[5]

Melatonin is a naturally occurring hormone produced by the pineal gland. Melatonin works by controlling the circadian rhythm and is used to improve sleep quality.

Who is melatonin funded for? Melatonin (brand name 'Circadin') will be funded from 1 July 2017 for children and young people up to the age of 18 years who have neurodevelopment disorders that make it difficult to sleep.

This is an "off-label" use which means that use is not registered with Medsafe (the part of the Ministry of Health that regulates medicines in New Zealand).

For more information on "off-label" use see the BPACnz article: Unapproved medicines and unapproved uses of medicines: keeping prescribers and patients safe.

How is melatonin funded? Melatonin is funded via a Special Authority and the person taking the melatonin must meet the Special Authority criteria to get funding.

The Special Authority allows melatonin to be funded for children and young people up to the age of 18 years who have neurodevelopment disorders that make it difficult for them to sleep.

The Special Authority must be applied for by a specialist, or a general practitioner on the recommendation of a specialist.

The specialists who can apply for a Special Authority are psychiatrists, pediatricians, neurologists or respiratory specialists, and the approval will last for one year so will need to be reapplied for each year.

You can find full details of the Special Authority criteria on the PHARMAC notification.

Special Authority cancellations - update 9 August 2017 Several Special Authorities have been approved via the Electronic Special Authority system for melatonin for people who don't meet the criteria because they are older than 18 years. We are working with the Ministry of Health to cancel these Special Authority approvals.

What does this mean for:

People whose Special Authority has been cancelled will need to talk to their prescriber.

Prescribers who have applied for melatonin Special Authorities where the patient does not meet the age requirements will be advised by Ministry of Health Sector Operations of the cancellations.

Pharmacy:

- **Prescriptions that have already been dispensed:** Pharmacies will be re-reimbursed for melatonin prescriptions that have already been dispensed and had a valid Special Authority at the time of dispensing.
- **New prescriptions:** If the patient is 19 years or older and has a Special Authority approval for melatonin, the Special Authority approval is not valid and their melatonin will not be funded.
- **Repeats**: If the patient is 19 years or older and has already collected their first month of funded melatonin prior to their Special Authority being cancelled, then that first dispensing is funded. However, any remaining repeats of melatonin will not be funded.

More information on Circadin use in children The Circadin brand of melatonin is the only brand of melatonin registered in New Zealand. It is registered for people aged 55 years or over. This means that its

[5] https://www.pharmac.govt.nz/medicines/my-medicine-has-changed/melatonin/

use in children is “off-label” (a use not registered with Medsafe) and needs to be discussed with a doctor.

PTAC (the Pharmacology and Therapeutics Advisory Committee that provides PHARMAC with objective clinical advice) has looked at the evidence for using melatonin in this group of children and young people and has recommended that it is funded. You can read more about the Committee’s most recent recommendation [PDF, 240 KB] at this link (starting on page 26).

The New Zealand Formulary for Children is a good place to go for information on melatonin use in children, including information on dosing. The New Zealand Formulary for Children can be found at www.nzfchildren.org.nz .

For more information on melatonin use in children see the BPACnz article: Melatonin is it worth losing any sleep over?

When should Circadin tablets be taken? The Circadin brand of melatonin is a modified-released tablet. This means the tablet is specially formulated to release the melatonin over a longer period and should be taken 1-2 hours before expected bedtime and after food.

Can Circadin tablets be halved? Circadin 2 mg modified-release tablet is meant to be swallowed whole and halving the tablets is not recommended by the supplier.

There is some evidence to suggest that when Circadin is halved it is still modified-release. This means it should be taken 1-2 hours before the expected bedtime, but since the supplier does not recommend halving the tablets it should be discussed with your doctor or pharmacist first.

See the article on Dissolution of Intact, Divided and Crushed Circadin tableta for more information.

What about crushing Circadin tablets? The BPACnz article advises that for children who are unable to swallow tablets the modified-release tablets can be crushed and mixed with a drink. This means the tablets would no longer be modified release and should be given immediately before bed time. Crushing the Circadin tablets is not recommended by the supplier and would need to be discussed with your doctor or pharmacist first. Last updated: 26 June 2018.

MCC 61st Meeting
AGENDA ITEM:

5.1.1 - Reclassification of modified release paracetamol – objection to the proposed recommendation that modified release paracetamol be reclassified from a pharmacy-only medicine to a restricted medicine

DATA TO SUPPORT OBJECTION RAISED TO A RECOMMENDATION MADE AT THE 60th MEETING OF THE MEDICINES CLASSIFICATION COMMITTEE, WELLINGTON, 26 APRIL 2018

Document type: **GSKCH Response to MCC 61st Meeting Agenda Item 5.1.1**

Submitted by: [redacted]
GlaxoSmithKline Consumer Healthcare, Australia and New Zealand

Release date: 17 September 2018

Number of pages: 22 Pages

Contents

Executive Summary

- The decision in Europe to suspend modified-release paracetamol products followed a complex Article 31 Referral procedure, which centred on concerns regarding modified-release paracetamol overdose raised by Sweden.
- The paracetamol overdose guidelines used in Sweden at the time of the referral (June 2016), upon which their concerns were based, are considered an inadequate basis upon which a decision in New Zealand should rely because those Swedish guidelines did not provide guidance on the treatment of overdose arising from the use of modified-release paracetamol (Salmonson et al 2018).
- Conversely, overdose guidelines designed to specifically address the considerations required with modified-release paracetamol have been in place in New Zealand since its first launch in this market in 2008 (Fountain et al 2014).
- The New Zealand paracetamol overdose treatment protocol is based on a paracetamol dose principal and is different to that used in Sweden.
- The European Commission agreed that the suspension might be lifted at a national level if Marketing Authorisation Holders could provide evidence of proportionate, feasible and effective measures to prevent the risk of overdose and minimise the risk for hepatic injury following intentional or accidental overdoses.
- Revised guidance for the management of modified-release paracetamol overdose, comprising five specific adaptations, has been sent out via a direct healthcare professional communication (MR-APAP DHPC, 2018), endorsed by European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC).
- All five of these PRAC-endorsed adaptations are already accounted for in the existing New Zealand guidelines. The current New Zealand paracetamol overdose guidelines already meet recognised best practice requirements.
- Like New Zealand, Denmark also has its own modified-release paracetamol overdose treatment protocol, which was established in 2013 (Andersen, 2013).
- Unlike in Sweden, the Danish and the New Zealand paracetamol overdose treatment protocols are based on a paracetamol dose principal and these guidelines already incorporate the principal elements of the PRAC best practice adaptations for modified-release paracetamol overdose treatment.
- On the basis of these established guidelines, the Danish Medicines Agency (Lægemiddelstyrelsen) has lifted the product license suspension and sale of modified-release paracetamol has been reinstated since 16 May 2018.
- Accessibility to means is considered to be a risk factor for self-harm. New Zealand and Denmark both have established overdose guidelines for the treatment of modified-release paracetamol overdose (based on similar principles) and neither country has had any reports of serious outcomes or deaths from overdose with modified-release paracetamol.

- Unlike in Sweden, high incidence rates of overdose with modified-release paracetamol have not been observed in New Zealand or in Denmark. Based on data available, in 2016-17, there was an average of:
    - **0.903 inquiries per 1 million modified-release paracetamol tablets sold** in **New Zealand** where modified-release paracetamol is a Pharmacy Only Medicine,
    - **3.614 inquiries per 1 million modified-release paracetamol tablets sold** in **Sweden** where modified-release paracetamol is a Prescription Only Medicine.
- The more restrictive medicines classification status in Sweden does not reduce the frequency of the incidence rates of overdose.
- This negates the proposition that reclassification to a Restricted Medicine may pre-emptively prevent higher incidence rates of overdose with modified-release paracetamol in New Zealand that have been observed elsewhere (e.g. Sweden).
- A core principle of any risk minimisation measure is that it should result in the right medicinal product being taken by right patient at the right dose and at the right time.
- Established best practice OTC medicine risk minimisation strategies – effective labelling, on-pack warnings, blister packaging, and pack inserts – are already in place for modified-release paracetamol products in New Zealand.
- One additional aspect of risk mitigation is to use package design to better help consumers differentiate between the different types of paracetamol products that are available in the Pharmacy in New Zealand.
- All Panadol packs incorporate evidence-based, consumer-focused labelling methodology to optimise the layout of information on the pack.
- To reinforce appropriate adherence to the recommended maximum daily dose of modified-release paracetamol,
- Combined, and in concert with the already demonstrated very low incidence of dosing error with modified-release paracetamol in New Zealand, these data provide reassurance

that consumers are able to appropriately self-select this product in a Pharmacy environment without having to be counselled by a Pharmacist, whilst knowing that a Pharmacist or Pharmacy Assistant is trained and readily available should questions arise.

- At the current Pharmacy-Only medicine classification, consumers are self-selecting modified-release paracetamol in an environment where they have an opportunity to seek advice from the Pharmacist should they need it. Based on the available data, reclassifying modified-release paracetamol to a Restricted Medicine, and thus mandating that all consumers receive counselling at every purchase of this product, is not likely to further mitigate an already very low risk of inappropriate use.

1 Introduction

At its 60th meeting (26 April 2018), the Medicines Classification Committee (MCC) discussed a proposal to reclassify modified-release paracetamol from pharmacy-only medicine to restricted medicine. In the MCC 60th meeting minutes (published 15 June 2018) it was recommended that this proposal be upheld.

Per the MCC processes, GlaxoSmithKline Consumer Healthcare (GSKCH) submitted an objection to this recommendation in which three separate reasons as grounds for objection were presented:

1. Practical differences between the paracetamol overdose guidelines in different countries
2. Current situation in Europe (Denmark)
3. [redacted]

Medsafe accepted the objection as valid on the basis that new information has been available and that the MCC did not consider all the safety and benefit issues correctly.

This document contains the relevant data supporting these grounds for objection for consideration at the MCC 61st meeting as agenda item 5.1.1 - Reclassification of modified release paracetamol – objection to the proposed recommendation that modified release paracetamol be reclassified from a pharmacy-only medicine to a restricted medicine.

2 Supporting data

2.1 Practical differences between the paracetamol overdose guidelines in different countries

2.1.1 Background to the objection

The decision to suspend modified-release paracetamol products in Europe followed a complex Article 31 Referral procedure in the European Economic Area (EEA) which centred on concerns regarding modified-release paracetamol overdose in Sweden, where high rates of overdose and complexities managing such paracetamol overdose cases had been identified as a safety issue.

Importantly, in giving its decision, the European Commission agreed that the suspension might be lifted at a national level if Marketing Authorisation Holders could provide evidence of proportionate, feasible and effective measures to prevent the risk of overdose and minimise the risk for hepatic injury following intentional or accidental overdoses.

Overdose guidelines designed to specifically address the considerations required with modified-release paracetamol have been in place in New Zealand since its first launch in this market in 2008 (Fountain et al 2014). Thus, guidelines to minimise the risk for hepatic injury following

intentional or accidental overdose with modified-release paracetamol are already established in New Zealand. However, two key questions remain:

1. How are they different from those used in Sweden?
2. Do they meet current best-practice guidance?

2.1.2 The established New Zealand guidelines are based on different principles to those used in Sweden

The paracetamol overdose guidelines used in Sweden, which led to the PRAC referral in 2016, are considered inadequate. As previously shown in the Salmonsson et al publication, the Swedish guidelines can lead to delays in treatment and/or put patients at risk of not being treated with the antidote (Salmonson et al 2018).

The crux of the current discussion therefore requires an understanding of how paracetamol overdose is managed differently in New Zealand. The Swedish guidelines state that antidote treatment (with acetylcysteine) should be given based on where a patient's blood level of paracetamol is relative to a line on a chart (called a nomogram). In contrast, the New Zealand paracetamol overdose guidelines state that antidote treatment (with acetylcysteine) should be given to all patients who have ingested a paracetamol dose >10 g (Chiew et al 2015), irrespective of whether it is a modified-release paracetamol or an immediate-release paracetamol.

These two different approaches can be called a "blood level approach" (used in Sweden) and a "paracetamol dose approach" (used in New Zealand). The differences between these two approaches and their consequences in terms of their ability to minimise the risk for hepatic injury following intentional or accidental overdoses are summarised below, specifically in relation to New Zealand and Sweden.

Sweden: Blood level approach	**New Zealand: Paracetamol dose approach**
• All patients presenting with a paracetamol overdose are required to have a blood test done before they are treated with the antidote. • Patients are only eligible to receive the antidote if the paracetamol level in their blood has reached a certain cut-off level on a chart. • There are two different cut-off lines, one for standard paracetamol and another one for modified-release paracetamol, which are applied depending on the paracetamol formulation taken.	• Treatment with the antidote is started immediately in all patients who have ingested more than 10g of paracetamol, irrespective of its formulation. • Patients who have ingested more than 10g of paracetamol are still required to have a blood test, but the result is effectively used to determine when to stop antidote treatment (not when to start it). • If overdose with modified-release paracetamol is suspected, additional blood tests are done to monitor response to extended treatment for the purposes of stopping treatment.

- The **limitations** of this approach are

(1) Patients have to wait until they have the results of a blood test before they can start treatment with the antidote.

(2) The emergency doctor needs to know how much time has elapsed since the overdose was taken to properly interpret the results of the blood test.

(3) The emergency doctor needs to know which paracetamol formulation has been taken to decide which cut-off line to use.

(4) There may be a greater risk of harm if modified release paracetamol has been used versus immediate release paracetamol, should that not have been considered.

- The **benefits** of this approach are

(1) Patients are treated with antidote immediately and this is continued until their blood test results indicate it can be stopped.

(2) The emergency doctor does not need to know which paracetamol formulation has been taken to decide on an appropriate initial course of action.

(3) There is effectively no greater risk in having modified-release paracetamol versus immediate release paracetamol.

The MCC meeting minutes state: *"The Committee discussed the difficulties of managing overdose with modified release paracetamol. There is a risk that paracetamol overdose may not be appropriately treated due to its slow release profile over time."*

- **Well-established treatment guidelines for overdose with modified-release paracetamol are established in New Zealand.**
- **The New Zealand paracetamol overdose treatment protocol is based on a paracetamol dose principal and is different to that used in Sweden.**

2.1.3 The New Zealand guidelines already meet the EMA PRAC guidance on the management of modified-release paracetamol overdose

When European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) decided to suspend the licences in the EEA, it also recommended, as an interim measure, revised guidance for the management of modified-release paracetamol overdose. This revised guidance was provided via a direct healthcare professional communication (DHPC).

In the EU, the marketing authorisation holder for the respective medicinal product usually disseminates a DHPC, either at the request of a competent authority in a Member State or the Agency, or at the marketing authorisation holder's own initiative (EMA Guidelines, 2017). The content and presentation of a DHPC disseminated by the marketing authorisation holder should be agreed with the (local) competent authority.

The modified-release paracetamol DHPC (MR-APAP DHPC, 2018) was send to healthcare professionals who treat patients with paracetamol overdose (e.g. Poison Information Centres,

emergency department hospital physicians, intensive care physicians, and general practitioners). Distribution commenced from the 19th March, 2018.*

The DHPC reinforced that protocols of blood sampling and treatment regimens (as used in the management of overdose with immediate-release paracetamol formulations) in many European markets (e.g. Sweden) are not adequate in cases of overdose with modified-release paracetamol. To address this, the letter provided five suggested adaptations to these standard protocols:

1. Where overdose with ≥10g of paracetamol (or ≥150 mg/kg body weight in children) is known or suspected, or where dose is unknown, treatment with antidote (N-acetylcysteine (NAC) should be started immediately regardless of the initial serum paracetamol level since serum paracetamol level in acute overdose with paracetamol modified release (MR) 665mg tablets might peak up to 24 hours after ingestion.
2. Where <10 g of paracetamol have been ingested and time since ingestion is known, multiple serum paracetamol samples should be taken at suitable intervals (e.g. 4, 6, and 8 hours after ingestion). Additional samples should be considered if serum paracetamol concentrations are not declining to low level. If serum paracetamol levels exceed the treatment nomogram at any time point, treatment with antidote (NAC) is indicated.
3. If time since ingestion is unknown or serum paracetamol concentration cannot be obtained within 8 hours of the overdose, it is recommended that treatment with antidote (NAC) should be initiated without waiting for serum paracetamol concentrations to be available.
4. If NAC treatment has been initiated, it should be prolonged beyond the first 21-hour NAC course if paracetamol level remains above the limit of detection (or greater than 10 mg/L) or if ALT is increasing (greater than 100 U/L), and should be continued until paracetamol is below the limit of detection (or 10 mg/L) or if ALT is falling below 100 U/L.
5. Antidote should be dosed as recommended by the local Poison Information Centre (include local contact details: Phone + Website + Email).

A comparison of the EMA PRAC suggested guidance and the wording in the current New Zealand guidelines has been undertaken (as detailed in the table below). All five of the EMA PRAC-suggested adaptations have already been accounted for in the existing New Zealand guidelines. As such, the current New Zealand paracetamol overdose guidelines already meet recognised best practice requirements.

* Mandated distribution to EEA markets in which modified-release paracetamol was marketed at the time (Belgium, Denmark, Finland, Luxembourg, Portugal, Romania, Sweden).

PRAC guidance	Wording in current New Zealand guidelines
• Where overdose with ≥10g of paracetamol (or ≥150 mg/kg body weight in children) is known or suspected, or where dose is unknown, treatment with antidote (N-acetylcysteine (NAC) should be started immediately regardless of the initial serum paracetamol level since serum paracetamol level in acute overdose with paracetamol modified release (MR) 665mg tablets might peak up to 24 hours after ingestion.	• If more than 200 mg/kg or 10 g (whichever is lower) has been ingested, acetylcysteine treatment should be started immediately. Serum paracetamol concentrations should be taken at 4 hours or more post-ingestion (as with standard preparations) and repeated 4 hours later.
• Where <10 g of paracetamol have been ingested and time since ingestion is known, multiple serum paracetamol samples should be taken at suitable intervals (e.g. 4, 6, and 8 hours after ingestion). Additional samples should be considered if serum paracetamol concentrations are not declining to low level. If serum paracetamol levels exceed the treatment nomogram at any time point, treatment with antidote (NAC) is indicated.	• If less than a toxic dose is ingested (10 g or greater than 200 mg/kg (whichever is lower)), serum paracetamol concentrations may be used to determine the need for acetylcysteine. Serum paracetamol concentrations should be taken at 4 hours or more post-ingestion (as with standard preparations) and repeated 4 hours later. If either concentration is above the nomogram line, acetylcysteine should be commenced.
• If time since ingestion is unknown or serum paracetamol concentration cannot be obtained within 8 hours of the overdose, it is recommended that treatment with antidote (NAC) should be initiated without waiting for serum paracetamol concentrations to be available.	• In patients in whom a paracetamol concentration cannot be obtained until 8 or more hours after ingestion, acetylcysteine should be commenced immediately, if the reported dose exceeds the threshold for possible toxicity. • If the time of ingestion is unknown, or the treating clinician is not confident of the history of ingestion, it is safest to treat the patient as a delayed presentation. Thus, the recommendation is to follow the > 8 hours scenario in Figure 2; that is to commence acetylcysteine.
• If NAC treatment has been initiated, it should be prolonged beyond the first 21-hour NAC course if paracetamol level remains above the limit of detection (or greater than 10 mg/L) or if ALT is increasing (greater than 100 U/L), and should be continued until paracetamol is below the limit of detection (or 10 mg/L) or	• Acetylcysteine may be discontinued if serial concentrations, taken 4 hours apart are below the nomogram line and are decreasing. Otherwise continue the full 21-hour course of acetylcysteine to its completion. • Near the completion of acetylcysteine the

if ALT is falling below 100 U/L.	patient should have a repeat ALT and paracetamol concentration. Acetylcysteine should be continued if the ALT is increasing (greater than 50 U/L) or paracetamol concentration is greater than 10 mg/L (66 μmol/L).
• Antidote should be dosed as recommended by the local Poison Information Centre (include local contact details: Phone + Website + Email).	*The New Zealand provides the currently endorsed recommendations for antidote administration (per below). Note that the Poisons Information Centre contact details are provided on the poster version of the guidelines.* • It is recommended that dosing tables providing the required volume of 20% acetylcysteine by weight, are used to chart the volume required in each infusion. This precludes the need for calculations and decreases the potential for error. Such tables are found in the acetylcysteine product information and have also been reproduced in this guideline (Table 4).

The MCC meeting minutes state: "*The MARC recommended at the 172nd meeting that the MCC consider reclassifying modified release paracetamol from pharmacy-only medicines to restricted medicines, and that guidelines for the treatment of modified-release paracetamol overdose be updated."*

- **The established New Zealand guidelines already incorporate all five of the PRAC best practice adaptations.**
- **Importantly, this reconfirms the position that the current protocol in place in New Zealand is considered best practice.**

2.2 Current situation in Denmark

2.2.1 Background to the objection

It is possible that the MCC may not have placed sufficient weight on the ability for current overdose treatment in New Zealand to manage modified-release paracetamol, given the comment in the minutes that *"[t]here is a risk that paracetamol overdose may not be appropriately treated due to its slow release profile over time".* However, it is the case that since 2008 when modified-

release paracetamol was first marketed, the New Zealand guidelines have included the management of modified-release paracetamol to ensure appropriate treatment.

While the MCC has been provided with information regarding the paracetamol overdose guidelines in Sweden and in New Zealand, they have not previously considered those in Denmark or taken account of the overdose guidance issued by EMA PRAC (discussed above). As such, the Committee has not had the opportunity to properly consider the safety implications of the current paracetamol overdose management guidelines available in New Zealand.

2.2.2 The Danish Medicines Agency has annulled the modified-release paracetamol marketing suspension

As is the case in New Zealand, Denmark also has its own paracetamol overdose treatment protocol, which was established in 2013 (Andersen, 2013). Having presented the details of this protocol to their local health authority, the protocol was found to be sufficient to enable an over-ruling of the PRAC recommendation. Consequently, on 16 May 2018, the **Danish Medicines Agency** announced an annulment of the European Commission marketing suspension on modified-release paracetamol. Modified-release paracetamol therefore remains on the market (Danish Medicines Agency, 2018).

The grounds for the decision to continue to allow the sale of modified-release paracetamol in Denmark were as follows:

- The Danish paracetamol overdose treatment protocol (Andersen, 2013) is different to that used in Sweden. Like the protocol in New Zealand, the **Danish protocol is also based on a paracetamol dose approach.** All patients are treated on suspicion of poisoning without waiting for a response from blood tests and the duration of antidote treatment is adjusted to the individual patient.
- Data from the "Giftlinjen" (the Danish Poisons Information Centre) do not demonstrate significant safety signaling related to overdose with modified-release paracetamol products in this market. [redacted]

[redacted]

2.2.3 The established New Zealand guidelines are based on similar principles to those used in Denmark and both meet the recent EMA PRAC guidance

The established New Zealand paracetamol overdose management guidelines are substantively similar to those used in Denmark; both rely on a paracetamol dose approach. In Denmark, there is a proactive overdose protocol for the treatment of overdose with paracetamol, where all patients are treated on suspicion of poisoning. Therefore, PRAC's justification for the recommendation to remove modified-release paracetamol from the market is not relevant in Denmark.

Importantly, as is the case in Denmark, the New Zealand guidelines are different to those in Sweden; they do not rely on establishing the paracetamol formulation taken or on blood test results before the antidote is given. The similarities between these two approaches are summarised below in relation to the PRAC guidance. Both sets of guidelines meet criteria specified for best practice in the management of overdose with modified-release paracetamol, as determined by PRAC.

EMA PRAC guidance	**Denmark: Paracetamol dose approach**	**New Zealand: Paracetamol dose approach**
1. Start antidote immediately in cases where overdose with ≥10g of paracetamol (or ≥150 mg/kg body weight in children) is known or suspected, or where dose is unknown.	✓ YES: If more than 6 grams (child > 125 mg/kg) has been ingested treatment is initiated immediately The limit of 6 grams is an estimate.	✓ YES: If more than 200 mg/kg or 10 g (whichever is lower) has been ingested, treatment is started immediately.
2. Where <10 g of paracetamol have been ingested and time since ingestion is known, take multiple serum paracetamol samples. If serum paracetamol levels exceed the treatment nomogram at any time point, treatment with antidote (NAC) is indicated.	✓ YES: If paracetamol poisoning is suspected, the patient is admitted to hospital. Immediate intravenous NAC treatment is initiated.	✓ YES: Serum paracetamol concentrations should be taken at 4 hours or more post-ingestion (as with standard preparations) and repeated 4 hours later. If either concentration is above the nomogram line, treatment should be started.
3. If time since ingestion is unknown or serum paracetamol concentration cannot be obtained within 8 hours of the overdose, treatment with antidote (NAC) should be initiated without waiting for serum paracetamol concentrations to be available.	✓ YES: If paracetamol poisoning is suspected, the patient is admitted to hospital. Immediate intravenous NAC treatment is initiated.	✓ YES: If paracetamol concentration is unknown or cannot be obtained until 8 or more hours after ingestion, treatment is started immediately.

4. If NAC treatment has been initiated, it should be prolonged beyond the first 21-hour NAC course if paracetamol level remains above the limit of detection (or greater than 10 mg/L) or if ALT is increasing (greater than 100 U/L), and should be continued until paracetamol is below the limit of detection (or 10 mg/L) or if ALT is falling below 100 U/L.	✓ YES: NAC infusion for 36 hours is recommended as standard treatment. Duration is adjusted to the patient: Can be stopped after 20 hours, based on clinically determined parameters. Can be stopped after three consecutive blood samples (taken 6 hours apart) based on clinically determined parameters.	✓ YES: A full 21-hour NAC infusion course is recommended with this being prolonged based on clinically determined parameters.
5. Antidote should be dosed as recommended by the local Poison Information Centre (include local contact details: Phone + Website + Email).	✓ YES: Specific guidance on NAC dosing is provided in the guidelines. Contact numbers provided.	✓ YES: Specific guidance on NAC dosing is provided in the guidelines. Contact numbers provided.

The MCC meeting minutes state: *"The Committee considered the classification of this product overseas and the situation in Europe. Modified release paracetamol products have been suspended in Europe until a harmonised guideline on managing overdose can be established."*

- **Unlike in Sweden, the Danish and the New Zealand paracetamol overdose treatment protocols are based on a paracetamol dose principal.**
- **The established Danish and New Zealand guidelines already incorporate the principal elements of the PRAC best practice adaptations.**
- **On the basis of these established guidelines, the Danish Medicines Authority has lifted the suspension and so re-instated the product licences permitting the sale of modified-release paracetamol.**

2.2.4 Situation in other European countries

The process to lift the marketing suspension on modified-release paracetamol is currently on-going in several other European countries. Key elements of this process include utilisation of the EMA PRAC overdose guidance (as discussed above) and the introduction of additional risk mitigation strategies such as blister packaging and consumer education. Both of these risk mitigation strategies have been in place in New Zealand for over 10 years.

2.2.5 Despite being in different medicines classifications, the incidence of overdose with modified-release paracetamol is very low in New Zealand and Denmark

Available local evidence supports the positive benefit-risk profile of modified-release paracetamol when used as indicated in New Zealand. Equally, there has been no suggestion of clinical concern regarding overdose cases or the management of overdose with modified-release paracetamol medicines in New Zealand. Data provided previously demonstrates a very low level of calls to the Poisons Information Centre in New Zealand. In the 10 years that modified-release paracetamol has been available in New Zealand, there have been 31 inquiries relating to this product.

Given that management of overdose with modified-release paracetamol was the primary impetus behind the EMA PRAC review, it is of value to compare the incidence of overdose in New Zealand versus that in Europe. To achieve this, the number of calls to Poisons Information Centres has been correlated with the sales data to obtain a common measure of the number of calls per 1 million modified-release paracetamol tablets sold. Available data for Sweden, Denmark and New Zealand for the year 2016-2017 are summarised below.

	Sweden	**Denmark**	**New Zealand**
Year	2016	2016-17	2016-17
Medicine Classification	Prescription	Prescription	Pharmacy Medicine
Number of calls to PIC			
Paracetamol	4391	-	1600*
Modified-release paracetamol	922	[redacted]	13
Proportion of paracetamol calls relating to modified-release paracetamol	**22%**	**-**	**0.4%**
Number of tablets sold	255,138,461	148,258,200	14,395,363
PIC inquires per 1 million tablets sold	**3.614**	[redacted]	**0.903**

PIC = Poisons Information centre.
* Calculated average based on all paracetamol calls made to New Zealand Poisons Information Centre between 1 Jan 2008 and 10 August 2016.
Data sources: Calls volume data for modified-release paracetamol sourced from MARC review report – 7 December 2017, correspondence with New Zealand PIC, and [redacted]. Sales data sourced from IMS data (sales to Pharmacy) for Sweden and Denmark and AC Nielsen data for New Zealand.

The above data demonstrates significant differences in the number of call and proportion of calls relating to modified-release paracetamol in these three markets. In Sweden there were 922 calls (22% of all paracetamol calls) in a year, whilst in New Zealand there were on average only 6-7 calls (0.4% of all paracetamol calls) and in Denmark there were on average only [redacted]. Thus, the lowest number of calls was in New Zealand, where this product has always been available over the counter as a Pharmacy-Only medicine.

This data shows that in 2016 and 2017 in New Zealand there was an average of **0.903 inquiries per 1 million modified-release paracetamol tablets sold.** This information is comparable to that observed in Denmark. In 2016 and 2017, "Giftlinjen" (the Danish Poisons Information Centre) had [redacted] regarding modified-release paracetamol. In the same time period, whilst there was a significant increase in sales of 665 mg modified-release paracetamol the inquiry trend remained consistent. Equating the number of calls with the sales volumes, demonstrates an average of [redacted]. Both Denmark and New Zealand display a significant difference to Sweden, where there was a 4-fold higher incidence of **3.614 inquiries per 1 million modified-release paracetamol tablets sold**.

Combined this information supports a comparable and very low incidence of modified-release paracetamol overdose, despite the difference in medicines classification and availability of modified-release paracetamol in New Zealand (Pharmacy Only, launched 2008) and Denmark (Prescription medicine, launched 2002). Both countries have established overdose guidelines and neither country has had any reports of serious outcomes or deaths from overdose with modified-release paracetamol. This is in stark contrast to Sweden. Despite modified-release paracetamol being available only on prescription in Sweden the rates of inquiries to the Poisons Information Centre were 4-fold higher than in Denmark and New Zealand.

Accessibility to means is considered to be a risk factor for self-harm. However, the data from Denmark and New Zealand provide compelling evidence that in two countries where best practice overdose guidelines are established differences in medicines classification status did not appear to have had impact on the incidence of overdose. This negates the proposition that reclassification may pre-emptively prevent higher incidence rates that have been observed elsewhere.

The MCC meeting minutes state: *"The Committee noted that in New Zealand immediate release paracetamol is more widely available than modified release paracetamol and that the incidence of paracetamol overdose due to modified release paracetamol in New Zealand is low compared to Europe. However, the Committee also discussed that reclassification may pre-emptively prevent higher incidence rates that have been observed elsewhere."*

- **Unlike in Sweden, high incidence rates of overdose with modified-release paracetamol have not been observed in New Zealand or in Denmark.**
- **Despite modified-release paracetamol being available only on prescription in Sweden the rates of inquiries to the Poisons Information Centre were 4-fold higher than in Denmark and New Zealand.**
- **The different medicines classification statuses in these markets do not appear to have impacted the incidence rates of overdose.**

2.3 Newly approved, re-designed packaging enhances product differentiation

Our original submission provided a number of risk mitigation strategies that could be considered by the Committee, in lieu of mandating Pharmacist counselling (as a restricted medicine). Of note, many established best practice risk minimisation strategies – effective labelling, on-pack warnings, blister packaging, and pack inserts – are already in place for paracetamol products in New Zealand.

A core principle of any risk minimisation measure is that it should result in the right medicinal product being taken by right patient at the right dose and at the right time. One aspect of risk mitigation is therefore to use package design to better help consumers differentiate between the different types of paracetamol products that are available over the counter for self-selection in the Pharmacy in New Zealand. Better differentiation would be expected to have a two-fold impact on modified-release paracetamol – firstly it would aid those consumers who need the benefits of a long-lasting pain reliever to identify this as a suitable product for their needs and secondly, in the event of an overdose, it would be more apparent that the product taken contained modified-release paracetamol.

All Panadol packs incorporate evidence-based, consumer-focused labelling methodology to optimise the layout of information on the pack. [redacted]

[redacted]

[redacted]

To reinforce appropriate adherence to the recommended maximum daily dose [redacted]

[redacted]

The MCC meeting minutes state: *"The Committee also discussed the risk of unintended misuse resulting in chronic overdose of modified release paracetamol which may result in long term liver damage. The Committee discussed the role of a pharmacist in counselling the patient on the appropriate use of modified release paracetamol, including dosage frequency"*

- **A core principle of any risk minimisation measure is that it should result in the right medicinal product being taken by right patient at the right dose and at the right time.**
- **Established best practice risk minimisation strategies – effective labelling, on-pack warnings, blister packaging, and pack inserts – are already in place for paracetamol products in New Zealand**

[redacted]

[redacted]

- **Combined, and in concert with the already demonstrated very low incidence of dosing error with modified-release paracetamol in New Zealand, these data provide reassurance that consumers are able to appropriately self-select this product in a Pharmacy environment without having to be counselled by a Pharmacist.**
- **At the current pharmacy-only medicines classification, consumers are purchasing modified-release paracetamol in an environment where they have an opportunity to seek advice from the Pharmacist or trained Pharmacy Assistant should they need it. Mandating that all consumers receive Pharmacist counselling at every purchase of this product is not likely to further mitigate an already low risk of inappropriate use.**

3 Concluding comments

The concerns raised by the Committee at the 60th MCC meeting were reflected in the minutes in terms of the "potential risks" for modified-release paracetamol products and were contextualised relative only to the situation in Sweden.

The paracetamol overdose guidelines used in Sweden are considered inadequate as they did not address modified-release paracetamol overdose treatment. The European Commission agreed that the suspension might be lifted at a national level if Marketing Authorisation Holders could provide evidence of proportionate, feasible and effective measures to prevent the risk of overdose and minimise the risk for hepatic injury following intentional or accidental overdoses. PRAC has subsequently endorsed guidance on how European countries should adapt their overdose guidelines to better equip them to manage cases of overdose with modified-release paracetamol.

Overdose guidelines designed to specifically address the considerations required with modified-release paracetamol have been in place in New Zealand since its first launch in this market in 2008 (Fountain et al 2014). All five of these PRAC-endorsed adaptations are already accounted for in the existing New Zealand guidelines. The current New Zealand paracetamol overdose guidelines already meet recognised best practice requirements.

Denmark (an EU member state) also has its own paracetamol overdose treatment protocol, which was established in 2013 (Andersen, 2013). On the basis of these established guidelines, the Danish Medicines Authority has now lifted the suspension on the sale of modified-release paracetamol. GSKCH therefore asks that the recent regulatory decisions in Denmark are reviewed and taken into account before any final recommendations are made locally.

Accessibility to means is considered to be a risk factor for self-harm. New Zealand and Denmark both have established overdose guidelines, based on similar principles, and neither country has had any reports of serious outcomes or deaths from overdose with modified-release paracetamol.

Unlike in Sweden, high incidence rates of overdose with modified-release paracetamol have not been observed in New Zealand or in Denmark. In 2016-17, there was an average of:

- **0.903 inquiries per 1 million modified-release paracetamol tablets** sold in New Zealand where modified-release paracetamol is a Pharmacy Only Medicine.
- [redacted]
- **3.614 inquiries per 1 million modified-release paracetamol tablets** sold in Sweden where modified-release paracetamol is a Prescription Only Medicine.

The different medicines classification statuses in in New Zealand versus Denmark do not appear to have impacted the already low incidence rates of overdose. This negates the proposition that reclassification may pre-emptively prevent higher incidence rates of overdose with modified-release paracetamol in New Zealand that have been observed elsewhere (e.g. Sweden).

A core principle of any risk minimisation measure is that it should result in the right medicinal product being taken by right patient at the right dose and at the right time. Established best practice risk minimisation strategies – effective labelling, on-pack warnings, blister packaging, and pack inserts – are already in place for Panadol paracetamol products in New Zealand. One additional aspect of risk mitigation is to use package design to better help consumers differentiate between the different types of paracetamol products that are available in the Pharmacy in New Zealand. This has been achieved [redacted]

The long-established overdose guidelines in New Zealand are considered global best practice, a low incidence of dosing error with modified-release paracetamol in New Zealand has been established and new updated product packaging has demonstrable ability to help consumers appropriately self-select based on the active ingredients. At the current Pharmacy-Only medicine classification, there is ample evidence that consumers are purchasing modified-release paracetamol in an environment where they have an opportunity to seek advice from the Pharmacist should they need it. Mandating that all consumers receive counselling at every purchase of this product is not likely to further mitigate an already very low risk of inappropriate use.

GSKCH retains its initial position that modified-release paracetamol has a favourable benefit-risk profile when supplied as a pharmacy-only medicine.

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18 September 2018

Medicines Classification Committee
Ministry of Health
By email: MCC Secretary at committees@moh.govt.nz

To the Medicines Classification Committee

Proposed reclassification of Circadin to a restricted medicine

The Pharmacy Council (Council) is a health regulatory authority established under the Health Practitioners Competence Assurance (HPCA) Act 2003. Council's primary role is to protect the health, safety and wellbeing of the public by ensuring pharmacists are competent and fit to practice.

One of Council's functions in section 118 of the HPCA Act 2003 is to set standards of clinical competence, cultural competence, and ethical conduct to be observed by health practitioners of the profession. Under this function Council has considered the application submitted by Aspen regarding the reclassification of Circadin to Prescription Medicine except when supplied in approved manufacturers' packs by a pharmacist who has undergone specified training on insomnia.

Council would like to make a submission in response to the Medicines Classification Committee's (MCC) consideration of an application from Aspen pharmaceuticals to reclassify Circadin as a restricted medicine for supply by a pharmacist.

Council will only comment on the competence of pharmacists to supply Circadin without prescription and will abstain from providing comment regarding the rationale for the reclassification itself. We make the following comments:

- Council considers pharmacists are competent to supply Circadin without prescription to patients meeting safety criteria specified by the Committee, and clearly outlined in validated screening tools. Any such tools would need to enable pharmacists to safely differentiate between primary and secondary insomnia, identify contra-indications to the use of Circadin, identify potential medicine interactions or exclusion criteria and provide clear messaging for referral of patients on to medical practitioners where necessary for patient safety.

- Pharmacists have a significant degree of knowledge around sleep hygiene and the use of non-prescription medicines, including restricted medicines to assist with insomnia. Community Pharmacists are often the first point of call for patients suffering with sleep disorders and are well-placed to provide patient counselling and screen for more concerning underlying medical conditions or causes/contributors to insomnia which may require referral to another health professional.

- Pharmacists have been supplying Circadin on prescription in New Zealand since 2012 and are therefore likely to have a degree of familiarity with the product and any patient counselling required to effectively support the patient in its safe use.

- Council agrees with the applicants proposed maximum period of Circadin supply as 13 weeks since this will provide opportunity for patients returning for repeat supply to be screened and if chronic use is determined necessary, referral to a medical practitioner facilitated to ensure detection of any underlying condition or initiate long-term management.

- As part of ensuring an accurate patient medication record is maintained for patients, we request mandatory retention of patient supply details in an electronic patient management system in a manner that can be shared where electronic sharing of patient information is facilitated, for example Health One or TestSafe. We would also request the Committee considers mandating the forwarding of supply details to the patient's GP to ensure the General Practice is aware of patient use of Circadin.

The Pharmacy Council appreciates the opportunity to comment on the application for reclassification of Circadin and welcomes further discussion regarding this proposal if necessary. We also request attendance at the meeting to discuss any proposed reclassification wording prior to gazette publication should the application be successful. We are concerned about requirements to supply manufacturers' original packaging as a requirement for legal supply of restricted medicines. A greater focus on patient information and appropriate labelling may more appropriately reflect patient safety and patient focused medicines management considerations.

Mandating the provision of manufacturers' original packs routinely in reclassification gazette notices, whilst providing a measure of assurance to the public around product source, does impact negatively on equity of access to medicines for some patients. It may also expose some patients to a greater risk of harm for those at risk of abuse, overuse or misuse of medicines.

We welcome further contact with MCC on this submission.

Your sincerely

Mark Bedford
Council Chair

C/O PO Box 5013
Wellington
New Zealand

MEDICINES ADVERSE REACTIONS COMMITTEE

18 September 2018

Chair, Medicines Classification Committee

Dear Chair, Medicines Classification Committee

Medicines Adverse Reactions Committee expression of support for the reclassification of modified-release paracetamol to restricted medicine

I am writing to you as Chair of the Medicines Adverse Reactions Committee (MARC). At the 175th meeting held on 13 September 2018 the Committee noted the objection to the MCC recommendation to change the classification of modified-release paracetamol from pharmacy-only medicine to restricted medicine. The Committee wished to make a submission to the MCC regarding this item.

The Committee did not consider that the objection from GSK provided any new safety information. The objection provided an update on the activities of the Danish Medicines Agency rather than any safety information informing these activities. It is noted that in Denmark, modified-release paracetamol is a prescription medicine.

The GSK objection also implied that the overdose guidelines in New Zealand are adequate to treat patients who may have overdosed with modified-release paracetamol. This view is not correct.

The risk of overdose with modified-release paracetamol was discussed by the MARC at the 172nd meeting on 7 December 2017. At this meeting, in addition to recommending that the MCC consider the classification of modified-release paracetamol, the MARC recommended that the New Zealand guidelines for paracetamol overdose be updated. The Committee has written to the guidelines group and they have agreed that the guideline is currently not adequate to deal with overdoses of modified-release paracetamol. The guidelines group are currently working to update the paracetamol overdose guideline.

The MARC strongly supports the original recommendation made by the MCC to reclassify modified-release paracetamol to restricted medicine, in the interests of patient safety. Please do not hesitate to contact me if you require any further information.

Yours sincerely,

Associate Professor David Reith
Chair, Medicines Adverse Reactions Committee
[redacted]

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20th September 2018

The Secretary, Medicines Classification Committee
Medsafe
PO Box 5013
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Sent by email: committees@moh.govt.nz

Re: Public Comment - Agenda for the 61st Meeting of the Medicines Classification Committee

We refer to the notice inviting public comment on items included on the agenda for the 61st meeting of the NZ Medicines Classification Committee (MCC).

ASMI (Australian Self Medication Industry) is the peak body representing companies involved in the manufacture and distribution of consumer health care products (non-prescription medicines) in Australia and New Zealand. ASMI also represents related businesses providing support services to manufacturers, including advertising, public relations, legal, statistical and regulatory consultants**.** We work closely with our sister organisation, the New Zealand Self Medication Industry Association (NZSMI).

The majority of the sponsors that market dextromethorphan and pholcodine in Australia also market these same products in New Zealand and are members of both ASMI and NZSMI. Most dextromethorphan and pholcodine containing products are harmonised across both markets as pharmacy medicines, with the same finished product characteristics as well as labelling where possible. The ability to market harmonised products is very important given that both Australia and New Zealand are relatively small markets individually. Some sponsors choose not to market unique Australian or New Zealand products, due to the detrimental impact on the cost of goods and the increased cost burden on consumers. A single product harmonised across both markets is important for economic viability.

Medsafe and the MCC acknowledge the importance of harmonisation and we refer in this context to the MCC's statement on general principles of Trans-Tasman Scheduling Harmonisation here.

We also refer the MCC to the submission made by NZSMI (New Zealand Self Medication Industry) and would like to make the MCC aware that any change to the classification of dextromethorphan or pholcodine in New Zealand will have an impact in Australia.

ASMI appreciates the opportunity to provide public comment in relation to item 6.2 of the agenda – the proposed reclassification from general sale and pharmacy only medicines to restricted medicines, for dextromethorphan, opium tincture, squill oxymel, and pholcodine. This submission will focus on dextromethorphan, pholcodine and squill oxymel. Opium tincture is a component of Gee's Linctus which is not marketed as an OTC medicine in Australia and is therefore out of scope of this submission.

In summary, ASMI's position is that:

In relation to Dextromethorphan:

- The classification of dextromethorphan should not be changed
- It is an opiate analogue, and has no analgesic activity as do the opiate analgesics. It is not addictive.

- The concerns regarding misuse and abuse are largely US-based, and in any event the US experience has shown that education has been an effective tool
- There is no evidence of problematic misuse or abuse in Australia and New Zealand. Reports have been very low in number and frequency
- Dextromethorphan continues to be available as a GSL / Pharmacy medicine in many countries with comparable regulatory standards as Australia/New Zealand
- Dextromethorphan products have been marketed for decades as single ingredient or in combination products. There have been no new or emerging safety signals during this time and there are no significant safety concerns that would alter the benefit/risk profile of dextromethorphan products

In relation to Pholcodine:

- The classification of pholcodine should not be changed
- Pholcodine is an opiate-like medicine however it is devoid of analgesic action. It has no addiction potential
- There is no evidence of concerns regarding misuse or abuse in Australia and New Zealand
- Pholcodine products have been marketed for decades in Australia, New Zealand, the UK and many other European countries, and there have been no new or emerging safety signals
- Regarding the hypothetical association between pholcodine use and anaphylactic reactions to neuromuscular blocking agents during surgery, there are many uncertainties and inconsistencies and a causative effect has not been demonstrated
- There are many other products that feature the molecular structure thought to be responsible for the reactions (quaternary ammonium ions) – these products include personal care items, cosmetics, disinfectants and many more and there is no certainty that pholcodine is the causative factor
- The EMA has reviewed the evidence and determined that no changes to access of pholcodine is needed due to the many uncertainties and inconsistencies in the available evidence

In relation to Squill oxymel:

- Squill and squill extracts are not related to opiates. The active components are more closely related to glycosides
- Oxymels are mixtures of vinegar and honey
- Squill extracts are permitted for use in listed complementary medicines in Australia and are not scheduled
- There is no available evidence that there are safety concerns with this compound and no evidence to support reclassification.

ASMI does not support the proposal to reclassify the above three medicines. The majority of consumers use these cough products safely and responsibly and there is no evidence of new safety concerns, misuse or abuse in New Zealand that would change the existing benefit/risk balance and trigger reclassification.

Any change to the classification in New Zealand would have consequences for Australia as it would significantly impact the ability of sponsors to supply harmonised products across both markets.

Thank you for considering this submission.

Yours sincerely

Australian Self Medication Industry Pty Ltd

Item 6.2: Dextromethorphan, opium tincture, squill oxymel, and pholcodine – proposed reclassification from general sale and pharmacy only to restricted medicine.

Overview

Medsafe's proposal to reclassify dextromethorphan, opium tincture, squill oxymel, and pholcodine appears to be based on concerns of "*easy availability of opioid (and opioid-like) cough medicines which can be bought at a pharmacy or supermarket without healthcare professional supervision*". The request for consideration of reclassification by the MCC refers to some specific concerns regarding misuse of dextromethorphan, misuse of Gee's Linctus, as well as the purported misuse of pholcodine. Reference is also made to the "Pholcodine hypothesis" and the postulated association of pholcodine with sensitisation to neuromuscular blocking agents (NMBAs).

Consumer safety is of paramount concern to ASMI and ASMI members, however we do not believe that the submission put forward by Medsafe justifies up-scheduling of squill oxymel, dextromethorphan or pholcodine.

Like all medicines, both dextromethorphan as well as pholcodine have risks and benefits. Labelling requirements and supply from a pharmacy can mitigate risk and pharmacists and pharmacy assistants also play an important role in educating consumers about risk. However, medicines can also have benefits – and consumers should be able to easily access medicines in order to relieve minor ailments that are recognisable and able to be self-managed by the consumer.

ASMI believes that Medsafe's proposal to reclassify squill oxymel, dextromethorphan and pholcodine to Pharmacist Only Medicine is regulatory over-reach and not consistent with the evidence provided in the submission.

For ease, this submission will address each of the active ingredients separately, based on the respective risks vs benefits associated with the substances and their uses.

We found the application to the MCC did not adequately differentiate the various concerns and are uncertain why oxymel squill has been included as part of the proposal to reclassify.

Need for OTC access of cough medicines as part of self-care

Acute cough is a prevalent condition, especially as it relates to the common cold. It is one of the most common reasons for visiting a pharmacy or self-selecting an OTC medicine. The majority of New Zealanders and Australians choose an OTC cough medicine to relieve cough; indeed self-care for symptoms of viral coughs and colds has been recommended in order to decrease utilisation of antibiotics (See NICE https://www.nice.org.uk/guidance/GID-NG10116/documents/draft-guideline).

Acute cough is regarded as a minor symptom and tends to be trivialised, but availability of cough relief is important because people's daily routines can be impaired by cough, for example night-time sleep disruption, hoarseness, being on public transport, and at work. In conditions such as post-viral inflammatory cough, the cough can be troublesome and persistent but not necessarily contagious, and access to effective OTC cough products can alleviate some of the discomfort. Consumers are familiar with navigating and self-selection in the pharmacy cough and cold category. Making changes to further restrict access could result in more people visiting their GP, which carries the attendant costs on the healthcare system and requests for sometimes inappropriate treatments such as antibiotics.

The Australian experience – Dextromethorphan and Pholcodine as Pharmacy Medicines

In Australia, all OTC medicines containing dextromethorphan and pholcodine are Schedule 2 (Pharmacy Medicines). As such, these products must be kept close to the pharmacy professional area, so that consumers can self-select under supervision from pharmacy assistants, but without the need for the pharmacist to be involved with every purchase. Pharmacists are available for advice if needed.

This arrangement seems to be successful in Australia. Consumers are generally familiar with the OTC cough category and the S2 schedule provides a level of supervision without the requirement for products to be hidden from view of consumers. We note that most dextromethorphan products are pharmacy medicines in New Zealand, with a small number of dextromethorphan products available as GSL medicines. All pholcodine products are pharmacy medicines.

The Australian Scheduling Factors for S2 medicines[1] are appropriate for cough/cold medicines that contain dextromethorphan or pholcodine. In ASMI's view the Australian experience with cough/cold medicines in S2 is positive with extremely low level of reports of misuse or abuse relative to the size of the market.

Adolescents who are curious about experimenting with a cough medicine are less likely to try and access it inappropriately if that they need to engage with a pharmacy assistant or pharmacist to purchase the product. Pharmacy assistants receive training and pharmacies that are QCPP accredited require pharmacy assistants to complete mandatory coursework[2]. PSNZ delivers similar programmes,[3] demonstrating that it is not necessary to restrict access to Restricted Medicine / Pharmacist Only to achieve quality use of medicines.

In Australia, dextromethorphan hydrobromide and pholcodine are included in OTC medicine monographs. Medicines that comply with the monograph may be registered through the OTC new medicines N2 pathway, with reduced evaluation by the TGA. Sponsors must comply with all aspects of the monograph in order to be allowed to use the N2 pathway. The TGA has therefore recognised the safety and efficacy of dextromethorphan and pholcodine in allowable preparations, under the conditions specified in the monograph (see https://www.tga.gov.au/otc-medicine-monograph-dextromethorphan-hydrobromide and https://www.tga.gov.au/otc-medicine-monograph-pholcodine).

Sales trends

ASMI is not able to obtain New Zealand sales data for dextromethorphan or pholcodine, however our understanding is that there have been no upwards trends in sales or unusual spikes in sales for Australia/New Zealand. Seasonal variations are a feature of sales for these products, with more products being sold during the cold and flu season than at other times of the year. There are also baseline sales during the summer months, as some people still get colds and upper respiratory tract infections during summer. Cough and cold is one of the most common presentations to the pharmacy.

ASMI and NZSMI members may be able to provide market data in their individual submissions to the MCC.

Opium tincture

Opium tincture is a component of Gee's Linctus. In Australia, opium tincture is a Schedule 8 substance in line with the other strong opiates such as morphine, pethidine etc. Consequently, Gee's Linctus is not available in Australia unless extemporaneously prepared on prescription.

[1] AHMAC Scheduling Policy Framework 2018. https://www.tga.gov.au/sites/default/files/ahmac-scheduling-policy-framework-medicines-and-chemicals.pdf
[2] Pharmacy Guild of Australia https://www.guild.org.au/guild-branches/wa/training/available-courses
[3] Pharmaceutical Society of New Zealand https://www.psnz.org.nz/Category?Action=View&Category_id=126

For this reason, ASMI has no comment on the classification of Opium tincture. It is reasonable for the MCC to consider the classification of opium tincture given that it contains small amounts of anhydrous morphine.

Squill oxymel

Squill extracts are allowed in Australia for use in listed / complementary medicines. The TGA's Permissible Ingredients Determination allows squill preparations to be used as an active ingredient in complementary medicines, see https://www.legislation.gov.au/Details/F2018C00499/Html/Volume_5 for details.

Squill does not contain any opiate or opiate like components, and its active components are more closely related to glycosides. Extracts and tinctures of squill have been used since medieval times as expectorants, in particular as squill oxymel. Oxymels are compounded preparations of honey and vinegar, thus squill oxymel consists of tincture of squill compounded with honey and vinegar.

ASMI can find no reason why oxymel squill has been included in the proposal to reclassify and we believe that a factual error has been made in the application, by assuming that the compound has opiate-like effects simply because it is a component of the Gee's Linctus formulation.

ASMI does not support any reclassification of squill compounds such as extracts or tinctures and Medsafe has not provided any evidence to support reclassification to Pharmacist Only / Restricted Medicine.

Dextromethorphan

The Medsafe submission to the MCC refers primarily to two concerns in its request for reclassification of dextromethorphan. These are:

- The opiate or opiate-like properties of dextromethorphan
- Reports of misuse and abuse – globally and locally

ASMI wishes to provide feedback on both of these concerns and provide relevant information on additional issues.

In the Discussion section of the Medsafe paper, references are made to community concerns about abuse of dextromethorphan and reports of misuse of dextromethorphan being made to Medsafe. ASMI is concerned with the lack of transparency and appropriate process, because:

- Details of these reports to Medsafe do not appear to have been included in the paper itself, unless these are the reports to CARM. This has not been properly explained.
- If there are community concerns or Medsafe concerns, discussion with the sponsors is a more appropriate first step than referring for reclassification
- Details of these community concerns have not been highlighted in the paper itself
- There is no evidence from sponsors corroborating any perceived community concerns

Opiate or opiate-like properties of dextromethorphan

The Medsafe submission to the MCC refers to dextromethorphan variously as "*not belonging to the opioid family but having a chemical structure closely resembling the opioids*" (page 1, section titled Purpose), then stating further in the document that "*DXM is an opioid*" (1st par, section titled *Background – Dextromethorphan and misuse*, page 1), and "*dextromethorphan is a weak opioid that can be subject to abuse*" (43rd meeting of the MCC, 13 April 2010). There appears to be some confusion as to whether dextromethorphan is an opiate, whether it has opiate like properties, and to what extent it is

pharmacologically similar to opiates. This confusion is not helpful and serves to inappropriately conflate dextromethorphan's pharmacological properties with those of other opiates.

While opiates such as codeine are used for pain, dextromethorphan has no analgesic activity and is used only for cough, a self-limiting acute condition.

The FDA has classified dextromethorphan as a non-narcotic cough suppressant. Although dextromethorphan is structurally similar to other morphine derivatives, it does not act as an opioid receptor agonist and is devoid of morphine-like effects[4, 5] . It is not included in the DEA's List of Controlled substances, available here.)

Following a 2012 pre-review of dextromethorphan conducted by the WHO Expert Committee on Drug Dependence (ECDD)[6], the committee concluded that a critical review of dextromethorphan was not warranted because of its medical usefulness and relatively low abuse liability[7]. The WHO has not included dextromethorphan in the list of substances under international control, available here.

Pharmacological actions

Dextromethorphan is a centrally acting cough suppressant. It is believed to suppress cough by altering the threshold for cough initiation through effects in the medulla oblongata[8]. While its pharmacology is not completely understood, dextromethorphan has been shown to bind to receptors implicated in the cough response, including the sigma-1 receptors and N-methyl-D-aspartate (NMDA) receptors.

At doses used for cough suppression, dextromethorphan has no effect on respiration, the cardiovascular system, the gastrointestinal tract, or mucociliary activity. It has little or no sedative or analgesic action.[6, 9, 10, 11, 12]

As stated in the Medsafe submission to the MCC, dextromethorphan toxicity occurs in a dose dependent fashion and at high doses it can exert mixed clinical psychoactive effects, eliciting both euphoria and dysphoria, distorted visual perceptions, loss of motor co-ordination, dissociative sedation and vomiting.

New Zealand & Australian market

As stated in the Medsafe submission, there are several dextromethorphan products available as GSL medicines in New Zealand, however most dextromethorphan products are marketed as Pharmacy Medicines, the majority of which are harmonised across both Australia and New Zealand.

ASMI members that supply the New Zealand market have advised that the vast majority of sponsors supply harmonised products, and for some sponsors, all of their dextromethorphan products supplied to the New Zealand market are harmonised. Some ASMI member companies have a policy of only supplying harmonised products and choosing not to supply unique Australian or New Zealand products if there are

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[5] Jasinski, D.R., 2000. Abuse Potential of Morphine/Dextromethorphan Combinations. Journal of Pain and Symptom Management 19 (No.1, Suppl. 1), 26-30.
[6] WHO ECDD review 2012
[7] WHO Reports of advisory bodies – Expert Committee on Drug Dependence. 35th meeting of the ECDD 4-8th June 2012. Report EB132/31, dated 23 November 2012.
[8] Canning B.J., 2009. Central Regulation of the Cough Reflex: Therapeutic Implications. Pulm. Pharmacol. Ther. 2009 April; 22(2): 75–81.
[9] FDA 1976. Food and Drug Administration. Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products. U.S. Department of Health and Human Services, Food and Drug Administration. Fed. Reg.1976; 41, 38338–40.
[10] Karttunen, P., Silvasti, M., Virta, P., Saano, V., Nuutinen, J., 1990. The Effects of Vadocaine, Dextromethorphan, Diphenhydramine and Hydroxyzine on the Ciliary Beat Frequency in Rats in Vitro. Pharmacology & Toxicology 67, 159-161.
[11] Bem, J.L., Peck, R., 1992. Dextromethorphan: An overview of safety issues. Drug Safety 7, 190-199
[12] Siu, A., Drachtman, R., 2007. Dextromethorphan: A review of N-methyl-D-aspartate receptor antagonist in the management of pain. CNS Drug Reviews 13, 96-106.

differences in classification or product details such as labelling, due to the implications of increased cost of goods associated with the more complex supply chain.

In Australia, dextromethorphan is available only as a Pharmacy Medicine, with the following scheduling criteria (see https://www.legislation.gov.au/Details/F2018L00625/Html/Text#_Toc512844863)

Schedule 2: DEXTROMETHORPHAN (excluding its stereoisomers) when supplied in a pack containing 600 mg or less of dextromethorphan and with a recommended daily dose of 120 mg or less of dextromethorphan.

Products supplied are either single ingredient liquids, or liquid and solid dosage forms containing dextromethorphan in combination with other active ingredients.

Overdose and misuse require consumption of large amounts of dextromethorphan, and this is difficult and unpleasant with liquid and combination solid dosage forms. Liquid products in particular are unpleasant if taken in large amounts, due also to the presence of excipients such as sorbitol.

Dextromethorphan has been available in New Zealand, Australia and globally for many years. In the US it has been available since 1958, so there are decades of marketing and safety experience with this medicine and it is one of the most widely used cough medicines globally. At recommended doses, it is recognised as having a good safety and efficacy profile.

Misuse potential

When conducting studies of drug abuse liability in humans, investigators include measures that reflect the likelihood of abuse, including subjective rankings of like/dislike, good/bad effects, mood changes, monetary value and others.[13] High doses (6 to 20 times the maximum therapeutic dose) of dextromethorphan can exert mixed clinical effects, eliciting both euphoria and dysphoria as well as psychedelic effects. These effects can also be associated with nausea and vomiting as well as "disliking" sensations in abuse liability evaluations. The "disliking" and dysphoria increase dose dependently.

These effects suggest a low potential for chronic abuse and are likely to contribute to limiting the appeal of dextromethorphan as a drug of choice for abuse. In the small number of studies conducted, dextromethorphan was found to produce neither opiate-like symptoms nor significant "liking" scores on the relevant scales used, and a more recent study has indicated that these effects may also be related to metaboliser status.[14,15]

Neither withdrawal nor tolerance appear to be factors in misuse or abuse of dextromethorphan. Case reports suggest that dextromethorphan does not produce physical dependence, but may induce psychological dependence, i.e. repetitive or compulsive behaviour apart from evidence of withdrawal or tolerance. Tolerance has been reported in a small number of case reports.[16, 17, 18, 19]

Overall, the results of human abuse liability studies do not characterise dextromethorphan as a substance that has very high abuse potential although it has been the subject of a small number of published case reports especially in the US. It has mixed effects including dysphoria and "dislike", suggesting that it may not be a preferred choice for abuse. Neither withdrawal nor tolerance appear to be strong factors in misuse

[13] Griffiths, R.R., Bigelow, G.E, Ator, N.A, 2003. Principles of initial experimental drug abuse liability assessment in humans. Drug and Alcohol Dependence 70. S41-S54.
[14] Jasinski DR. Abuse potential of Morphine/Dextromethorphan Combinations. Journal of Pain and Symptom Management 2000;19(1):26-30
[15] Zawertailo L.A, Tyndale R.F, Busto U, Sellers E.M. Effect of metabolic blockade on the psychoactive effects of dextromethorphan. Human Psychopharm. 2010;25:71-79
[16] Cranston, J.W., Yoast, R., 1999. Abuse of dextromethorphan. Arch. Fam. Med. 8, 99-100
[17] CESAR, 2007. Drug information: DXM. http://www.cesar.umd.edu/cesar/drugs/dxm.asp
[18] Schwartz, R.H., 2005. Adolescent abuse of dextromethorphan. Clin. Pediatr. 44, 565-568;
[19] Miller, S.C., 2005. Dextromethorphan psychosis, dependence and physical withdrawal. Addiction Biology 10, 325-327.

and abuse of dextromethorphan, with these effects more apparent with frequent ingestion of high doses. This suggests low potential for dependence.

New Zealand concerns regarding dextromethorphan

The Medsafe submission has not provided strong evidence of a New Zealand specific problem of misuse / abuse of dextromethorphan. It includes the following primary evidence:

- Three case reports from the CARM database, two from 2009 and one from 2011. The last report to CARM was 7 years ago. None of these cases involved adolescents. No details are cited as to whether there was concurrent misuse of other drugs. The relationship between dextromethorphan and the reactions recorded were probable or possible. There are unknown factors which include the doses taken of the medicines.
- Reports to the National Poisons Centre (NPC): For Gee's Linctus, dextromethorphan (either single ingredient or combination products) and pholcodine (either single ingredient or combination) – there were 18 calls between August 2011 and June 2018, (i.e. a period of 7 years), that were classed as "abuse" or "intentional". This averages out to fewer than three cases per year over the 7 years.
- Neither of these sources suggest that there is ongoing or escalating abuse/misuse
- The National Poisons Centre (NPC) data stated that all 18 reported cases over the reported 7-year period resulted in medical referral. It would be assumed that had a genuine public health concern been detected, the medical practitioners / healthcare professionals would have made the relevant notifications. There is no information to suggest that this has taken place either recently or in the past.

The submission states that it is hard to find useful measures of abuse in New Zealand and that the reports may not reflect the true extent of abuse/misuse. This assertion may or may not be true, however ASMI suggests that these reports from CARM and the NPC on their own do not reflect a public health problem with dextromethorphan in New Zealand and the MCC should not consider reclassification based on these reports.

Considering the high volumes of sales of these products, the reports appear to be both infrequent and isolated.

Sponsors have obligations to record and monitor adverse events as well as report serious adverse events under their pharmacovigilance responsibilities, in Australia as well as in New Zealand. The New Zealand Medicines Act 1981 places responsibility on sponsors to report untoward effects of medicines and sponsors take these responsibilities seriously. Medical practitioners and treating hospital staff report adverse events to the sponsors, and sponsors comply with their reporting obligations to Medsafe and the TGA as appropriate.

By way of example, in Australia, of the 18,600 total adverse event reports received by the TGA in 2017, approximately 54% (9998) were from sponsors; 18% (3441) from State and Territory Health Departments (reports of adverse events following immunisation); 10% (1879) from hospitals and hospital pharmacists; 7% (1201) from consumers; 6% (1170) from community pharmacists; 3% (579) from general practitioners (GPs); and 2% (359) from other sources[20]. We believe that sponsors would comply with their reporting responsibilities to Medsafe in a similar manner.

In ASMI's opinion, we do not accept the view expressed in the paper that three reports to CARM and isolated calls to the National Poisons Centre on their own are indicative of a major concern with misuse or abuse.

[20] https://www.tga.gov.au/medicines-and-vaccines-post-market-vigilance-statistics-2017

There is an expectation that a change to classification should be based on robust evidence of a significant problem. It should identify the extent of the problem, where the problem is occurring, the relevant products and the sources of purchase (pharmacy or grocery). It should identify clearly the characteristics of people who have misused/abused the medicines and the resulting health consequences, as well as describe how reclassifications is the most appropriate means of addressing any identified concerns. Classification is an assessment of benefit vs risk, and we believe that the specific risks in NZ have not been clearly articulated and there is no justification for justify imposing restrictions on access.

Australian experience and adverse event reports

As stated in the overview, dextromethorphan is a pharmacy medicine in Australia. There is no evidence of widespread abuse or misuse of dextromethorphan.

Pharmacists and pharmacy assistants monitor product sales.

We have conducted a search of the Australian Database of Adverse Event Notifications (DAEN), for the entire period of 1971 until June 2018. The results are summarised below:

- The search covered 53 products. Some of these have been discontinued over the years
- The search period covered 1971 – June 2018 (47 years)
- Over this period there were 283 reports, with 258 of these where dextromethorphan was the single suspected medicine
- 3 cases of overdose; one of these resulting in death
- 2 cases of intentional product misuse
- 2 cases of drug dependence
- 1 case of intentional overdose
- Other reported adverse events involved eye disorders, gastrointestinal disorders, general disorders, immune, infections, psychiatric, skin disorders, CNS and respiratory
- There appeared to be no specific trends, however the most common reports were CNS and psychiatric as would be expected for a centrally acting medicine.

Considering the very high volumes of product used over the past 47 years, the Australian DAEN reports do not indicate that there are any new risks or trends that ought to trigger any changes to the classification of the medicine.

ASMI also reviewed the most recent annual report of the Australian Poisons Information Centres[21] as well as the 2013 Annual Report of the NSW Poisons Information Centre[22], which is the most recent annual report published. Cough and cold medicines were not included in the list of the ten most frequent calls, despite their accessibility. There was no discussion of cough and cold medicines in either of these reports.

ASMI does not believe that there have been any new or emerging safety signals for dextromethorphan.

Previous considerations by NDPSC and MCC

According to the Medsafe submission, dextromethorphan was considered by the MCC at the 21st meeting (1999), 27th meeting (2002), 29th meeting (2003), 30th meeting (2003), 37th Meeting (2007), and 43rd meeting (2010).

At four of the above meetings, the MCC considered the GSL classification in New Zealand, and determined that there was no new evidence to justify changing the NZ classification of dextromethorphan. In 2002, the MCC declined a request to harmonise with Australia (at the NDPSC request) and this decision was again

[21] Huyn A, Cairns R, Lynch A-M, Robinson J, Wylie C, Buckley NA, Dawson AH. Patterns of poisoning exposures at different ages: the 2015 annual report of the Australian Poisons Information Centres. MJA 2018; 209(2):74-78
[22] https://www.poisonsinfo.nsw.gov.au/site/files/ul/data_text12/4918535-NSWPIC_Annual_Report_2013.pdf

confirmed in 2007. We note that two reports were made to CARM in 2009, and these reports were considered at the 2010 meeting, at which again there was no decision to change the classification. There have been no more reports to CARM since 2011.

Based on the evidence presented with the submission there does not appear to be any new evidence that could justify a shift in that position given that there is no new conclusive evidence of any change to the risk profile of dextromethorphan.

Overseas Regulatory Actions

Of the key regulatory agencies that have recently considered the classification of dextromethorphan and have conducted thorough reviews, all have decided to make no changes to classification, except perhaps for a small number of individual states.

Canada

In Canada, dextromethorphan was considered for review by the Canadian Scheduling authority (NAPRA) following the recommendations in a 2011 Coroner's report on two deaths in which accidental overdose with cough medicines containing dextromethorphan was considered to be a factor.

Following a review, there was no change to access in Canada and dextromethorphan is classed as unscheduled (GSL) when in oral dosage forms in package sizes containing no more than 300 mg dextromethorphan and as an OTC Pharmacy Medicine (equivalent to NZ Pharmacy Medicine) for pack sizes above this limit, in all states except Quebec.

USA

In 2010, the FDA announced a meeting of the Drug Safety and Risk Management Advisory Committee to discuss the abuse potential of dextromethorphan and the public health risks and benefits of this medicine. The scientific review and medical evaluation also reviewed whether scheduling of dextromethorphan under the Controlled Substances Act was warranted.

The outcome of the review was that the potential risks of abuse among teenagers did not warrant restricting dextromethorphan and the classification of dextromethorphan remained unchanged. It was not scheduled as a controlled substance.

Dextromethorphan is classed as an OTC medicine in the US, which means that it is available for general sale in various strengths and dosage forms (there is no Pharmacy Medicine or Pharmacist Only Medicine classification in the USA).

The US Consumer Healthcare Products Association (CHPA) conducted an educational and social media campaign following the FDA Advisory Committee meeting in 2010 and while a true cause-and-effect relationship cannot be assured the annual prevalence of over-the-counter cough medicine abuse has sharply decreased since then[23].

Karami et al[24] looked at reports of intentional abuse of DXM over a 15-year period (2000-2015). Rates of abuse in adolescents (14-17 years) steadily decreased from 2006 onwards. Overall, rates of abuse in adults were observed to be lower than in adolescents. Whilst rates of abuse in adults aged 18-21 years did not change significantly over the period 2006-2015, the rates of abuse in adults aged 22-29 years steadily and continually increased over this same period.

[23] Spangler et al. Dextromethorphan: a case study on addressing abuse of a safe and effective Drug. Substance Abuse Treatment, Prevention, and Policy (2016) 11:22

[24] Karami S, Major JM, Calderon S, McAninch JK. Trends in dextromethorphan cough and cold products: 2000–2015. National Poison Data System intentional abuse exposure calls. Clinical Toxicology 2018;56(7): 656–663

The Medsafe submission refers to the FDA Safety Alert on codeine / hydrocodone, and we note that the dextromethorphan is mentioned in this Alert as an example of products that are suitable for use to treat cough, so that codeine can be avoided.

It is apparent that abuse and misuse was an acknowledged concern in the US, however the action that was taken was an educational campaign, primarily using social media. This has had reasonable success, with an overall downward trend of abuse and misuse especially in adolescents.

Europe

In 2016, the European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC) conducted a review of the safety and efficacy of dextromethorphan. Based on the review, the risk-benefit balance of dextromethorphan-containing medicinal products in the approved indications remains unchanged[25]. PRAC recommended updates to the Patient Information Leaflet and Summary of Product Characteristics to inform of the risk of abuse as well as a warning about the possible interaction with cytochrome P450 2D6 (CYP2D6) inhibitors.

Most European countries have retained the non-prescription status of dextromethorphan – including Finland, Germany, Italy, Portugal, Spain, Switzerland, Netherlands and the UK, although there are a small number of exceptions. Dextromethorphan is not registered or marketed in Sweden and was reclassified to prescription in Denmark (2008) and France (2017), due to local reports of misuse/abuse[26]. Dextromethorphan is a Pharmacy Medicine in the UK.

WHO Review

In 2012, the WHO Expert Committee on Drug Dependence conducted a comprehensive review of dextromethorphan and considered its convertibility into controlled substances, as well as its toxicology, dependence potential and abuse potential. No changes to the status of dextromethorphan were made following this review and it was not included in the international list of controlled drugs[8].The report concluded that additional controls were not warranted because of its medical usefulness and relatively low abuse potential.

Pholcodine

Medsafe has requested the MCC to consider the classification of pholcodine, proposing that it consider reclassifying from pharmacy medicine to restricted medicine primarily because of:

- Potential for misuse
- Possible association between pholcodine use and anaphylactic reactions to neuromuscular blocking agents (NMBAs) during surgery.

This response will discuss both of these concerns.

Pholcodine was developed in the 1950s, and the clinical studies are not well designed and controlled by today's standards. However, after more than 50 years of marketing experience and widespread use without significant safety concerns the body of evidence that is currently available shows that:

- Pholcodine is not converted to morphine in the body to any extent that would have clinical significance. Some studies have found no conversion to morphine, while another study has found conversion to trace levels

[25] http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2016/09/WC500213110.pdf (see item 6.3.4 for dextromethorphan)
[26] Association of the European Self Medication Industry (AESGP) Economic and Legal Framework Database. http://www.aesgp.eu/facts-figures/

- There is no evidence of addiction potential
- There is no evidence that tolerance occurs
- Pholcodine has an antitussive potency about 1.6 times that of codeine and one which is more highly specific, since it has little if any analgesic action compared to codeine (Cahen & Boucherle, 1961a; Kelentey et al., 1958).
- Pholcodine has a more favourable safety profile than codeine and does not share the same safety concerns and adverse events.

Opiate or opiate-like properties and metabolic pathways

Pholcodine (3-O-(-2'-morpholinoethyl)-morphine) is an opiate-like medicine with central antitussive action, but no analgesic properties and no evidence of addiction potential.

Although a study in rats found evidence that morphine is a minor metabolite of pholcodine, accounting for less than 1% of the dose, this has not been consistently observed in human studies. Two studies conducted in humans, one single dose pharmacokinetic study, and one study testing single and chronic dosing over 10 days, could not detect any morphine in urine even after enzymatic hydrolysis.[27, 28]

In the pharmacokinetic study conducted by Chen[26], none of the subjects experienced any of the usual opioid-like side effects such as constipation, urinary hesitancy, drowsiness, dizziness, nausea and confusion even though pholcodine was administered over 10 days.

A paper by Maurer and Fritz (1990) [29] describes the metabolism of the antitussive 3-O-(-2'-morpholinoethyl)-morphine (pholcodine, Tussokon) in man. The metabolites were identified after cleavage of conjugates, extraction and derivatization by acetylation in human urine using gas chromatography-mass spectrometry. The following seven metabolites could be identified besides the unchanged pholcodine: Nor-P, desmorpholino-hydroxy-P, nor-desmorpholino-hydroxy-P, hydroxy-P, oxo-P, nor-oxo-P and morphine in traces.

Pholcodine is therefore highly unlikely to exert its pharmacological effect via conversion to morphine.

New Zealand & Australian markets

Pholcodine has been available in Australia and New Zealand for more than 30 years. It is available as a pharmacy medicine in New Zealand and as a Schedule 2 medicine in Australia.

Similarly to dextromethorphan, it must be stored in the professional area of the pharmacy where sales are supervised by a pharmacy assistant and the pharmacist is available to provide advice when required.

We note that the Medsafe submission has omitted reference to a large number of pholcodine containing products that are available in New Zealand and harmonised with Australia. Marketed products that the Medsafe paper neglected to mention include:

- Benadryl Dry Tickly Cough (however ASMI understands that this has been recently discontinued)
- Difflam Anti-inflammatory Lozenges with Cough Suppressant, Blackcurrant Sugarfree
- Duro-Tuss Cough Liquid Expectorant Oral Solution 0.8 mg/1 mg per mL
- Duro-Tuss Dry Cough Lozenge (Lemon) (cetylpyridium; pholcodine)

[27] Findlay, J. W. A., Fowle, A. S. E., Butz, R. F., Jones, E. C., Weatherley, B. C., Welch, R. M. & Posner, J. (1986). Comparative disposition of codeine and pholcodine in man after single oral doses. Br. J. clin. Pharmac., 22, 61-71.

[28] Chen ZR, Bochner F, Somogyi A. Pharmacokinetics of pholcodine in healthy volunteers: single and chronic dosing studies. Br. J. clin. Pharmac. (1988), 26, 445-453

[29] Maurer HH, Fritz CF. Metabolism of pholcodine in man. Arzneimittelforschung. 1990 May;40(5):564-6 https://www.ncbi.nlm.nih.gov/pubmed/2383296

- Duro-Tuss Dry Cough Lozenge (Orange) (cetylpyridium; pholcodine)
- Duro-Tuss Dry Cough Liquid Forte Oral Solution, 3 mg/mL (pholcodine)
- Duro-Tuss Dry Cough Liquid Junior Oral Solution, 1mg/mL (pholcodine)
- Duro-Tuss Dry Cough Liquid Regular Oral Solution, 1mg/mL (pholcodine)
- Duro-Tuss Phenylephrine PE Dry Cough + Nasal Decongestant Oral Solution (phenylephrine; pholcodine).

Any changes to the classification of pholcodine will therefore have a significant impact on a large number of harmonised products.

Issues regarding the importance of harmonisation have been raised earlier in this submission in relation to dextromethorphan, and the principle applies equally for pholcodine.

ASMI believes that pholcodine has had a long history and a well-established, favourable safety profile. A search of the TGA Database of Adverse Event Notifications (DAEN) was conducted, for the period 1971 until June 2018. Some key points from the results of this search are:

- The search covered 24 products, some of which included combinations that are no longer available and products that have been discontinued
- Over this period, there were 185 adverse event reports, with 138 being reports from a single suspected medicine
- There were no reports of intentional product misuse
- There were no reports of drug dependence
- There were no reports of intentional or unintentional overdose
- There was one death, with the event reported to be a cardiovascular disorder described as arteriosclerosis coronary artery (sole suspected drug)
- There was one death described as toxicity to various agents, and pholcodine was not the sole suspected drug
- The most commonly reported adverse events involved general disorders, gastrointestinal disorders, nervous system and psychiatric, skin disorders, respiratory disorders
- There were no observed patterns of misuse, abuse or other adverse event trends

Considering the high volume of products used over the past three to four decades, the Australian DAEN reports do not indicate any new safety concerns or trends that ought to trigger any change to the classification of the medicine.

As per the comments included for dextromethorphan, the NSW Poisons Centre and Australian Poisons Centre's last two annual reports did not discuss cough and cold medicines at all.

ASMI does not believe that there are any new or emerging safety signals for pholcodine.

Concerns regarding potential for misuse or abuse of pholcodine New Zealand

The Medsafe submission to the MCC makes the assertion that pholcodine (together with dextromethorphan, and anhydrous morphine), "*could all potentially be misused*" (see Discussion, last page; submission was not paginated).

ASMI is concerned at this statement. It conflates morphine, an opiate which is a highly effective and addictive analgesic with recognised potential for misuse and significant central effects, with dextromethorphan and pholcodine, which have been marketed in the GSL (in the case of dextromethorphan only) and in pharmacy for cough. The statement implies that all three of these medicines have a similar potential for misuse. This statement is an assertion that cannot be justified based on available evidence.

To our knowledge, there are no reports of misuse or abuse of pholcodine reported to the New Zealand CARM.

Morphine cannot be extracted from available cough suppressant medicines without a high level of knowledge, equipment and sophistication. Many of these medicines are combinations with other cough/cold medicines and extraction from multi-ingredient liquid formulations would be extremely difficult to achieve. There is no evidence presented in the submission that extraction of morphine from pholcodine is occurring.

There is no specific New Zealand information included in the submission, that supports the premise that there is misuse of pholcodine in the community, and that if present, it could possibly be comparable with any misuse of anhydrous morphine.

"The Pholcodine Hypothesis": Pholcodine and anaphylactic reactions to Neuromuscular Blocking Agents

The Medsafe submission also refers to the hypothetical association between severe allergic reactions to neuromuscular blocking agents during surgery and previous pholcodine exposure. This issue is discussed in the Medsafe submission, referring to the recent action taken by the French regulatory agency (AFSSAPS; now the ANSM).

ASMI acknowledges these concerns, however we believe that at present there are unresolved issues and though there may be hypothetical links, the evidence has not shown a causal relationship between pholcodine use and anaphylactic reactions to NMBAs.

The concerns are based on observations performed over several years by a Swedish / Norwegian team of researchers who found that withdrawal of a particular pholcodine containing product (Tuxi) in Sweden and Norway resulted in an apparent decrease in reports of NMBA related anaphylaxis.

The European Medicines Agency published an assessment report for pholcodine in 2012[30], reviewing the safety and efficacy of pholcodine as well as the pholcodine-NMBA anaphylaxis hypothesis.

The key findings of this review were that:

"*the evidence in support of an association between pholcodine and NMBS related anaphylaxis is circumstantial, not entirely consistent and does not support the conclusion that there is a significant risk of cross-sensitisation to NMBAs and subsequent development of anaphylaxis during surgery. Further data needs to be generated to clarify the possibility of an association between pholcodine use and NMBA-related anaphylaxis*."

The report concluded that the benefit/risk balance of pholcodine-containing products in the treatment of non-productive cough is positive under normal conditions of use, and that no changes to access were required. Regarding the hypothetical association between pholcodine and anaphylaxis to NMBAs, the EMA believes that further research is required as there are inconsistencies that do not support the association.

<u>Uncertainties</u>

There are some uncertainties and inconsistencies that are difficult to reconcile with the pholcodine / NMBA anaphylaxis hypothesis.
There is strong evidence that quaternary ammonium ions (QAI) are the allergic determinants in NMBAs. These molecules are present in many other drugs as well as foods, cosmetics, disinfectants, and industrial materials. It is possible that predisposed individuals may be sensitised to undetermined QAI and thus potentially be at risk. The possible causative factor(s) are uncertain and the possibility remains that

[30] EMA/78398/2012 Assessment report for Pholcodine containing medicinal products. February 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Pholcodine_31/WC500124716.pdf

unrecognised environmental factors may play a role. There is a wide range of possible sources for sensitisation to NMBAs[31].

There are some additional concerns with the hypothesis. The gender difference between males to females (from 2:1 to 4:1) is unexplained; it is possible that there are other factors involved such as an environmental trigger (e.g. cosmetic use).

In a study investigating the prevalence of specific IgE to quaternary ammonium ions in two populations professionally exposed to quaternary ammonium compounds in the north-eastern France, it was found that exposure to hairdressing professional occupational factors, such as quaternary ammonium ion hairdressing products, increased IgE-sensitization to NMBAs compared to bakers and a control group, indicating that occupational and environmental exposure to these compounds may be a factor[32].

In a multicentre study that examined the pholcodine hypothesis[33], the consumption of pholcodine containing cough medicines was compared to the prevalence of IgE antibodies to pholcodine, morphine and suxamethonium (a NMBA). The findings showed some inconsistencies, in that the Netherlands and the USA that do not have pholcodine products on the market, had some high figures of IgE sensitisation. The USA, where no pholcodine is consumed, showed similar levels of IgE sensitivity as the UK, where pholcodine is readily available and widely used as an OTC cough suppressant. Of the four countries with antibodies to suxamethonium, two (the USA and Germany) have no pholcodine consumption.

The incidence of anaphylaxis in surgery is extremely low. Some studies based in Australia and France have estimated the overall incidence to be between 1 in 10,000 and 20,000 procedures. The low number of reports can present difficulties in studying the effects of individual drugs.

The EMA, in its 2012 review, concluded that the existing evidence for risk is weak and that the benefits of pholcodine continue to outweigh its risks. ASMI believes that the evidence base for consideration of reclassification to Pharmacist Only medicine is weak. The EMA did not recommend reclassification in 2012, and since the time of publication of the EMA review no new evidence has come to light that would change that conclusion.

Overseas Regulatory Status

- Pholcodine is marketed as a Pharmacy Medicine in Australia, New Zealand, the UK and Belgium
- It is a prescription medicine in and France
- It is not marketed in Canada, the USA, Germany, Portugal, Greece, Spain

[31] Mertes PM et al. Hypersensitivity reactions to neuromuscular blocking agents. Curr Pharm Des. 2008;14(27):199-211
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20 September 2018

The Secretary
Medicines Classification Committee
Medsafe
P.O. Box 5013
WELLINGTON 6145

Sent by email: committees@moh.govt.nz

Re: Public Comment - Agenda for the 61st Meeting of the Medicines Classification Committee

Item 6.2: Proposal for reclassification of cough medicines containing dextromethorphan, opium tincture, squill oxymel and pholcodine to restricted medicines

Executive Summary

iNova Pharmaceuticals (iNova) do not support the proposal to reclassify pholcodine or other referred to cough medicines to restricted medicine status. Evidence to support the proposition that medicines containing pholcodine are abused or that potential for abuse exists is unavailable. The pharmacology of pholcodine, the difficulty of extracting pholcodine from a cough medicine and the absence of adverse event reports provide evidence that pholcodine is not abused or likely to be abused. Concerns regarding the possibility of a rare association between pholcodine use and NMBA-related anaphylaxis are circumstantial. Neither the EMA nor TGA who have previously reviewed this matter recommended changes to pholcodine access.

The current pharmacy only medicine classification which has been in place for many years provides adequate supervision of patients who need advice on management of their cough and the appropriate use of cough medicines. Further restrictions only create greater difficulties for patients to readily access medicines which provide relief from cough without creating any additional overall public health benefit.

iNova recommend retention of the current classification of pharmacy only medicine for pholcodine and also support the status quo for other cough medicines referred for reclassification.

Introduction

iNova wish to comment on the NZ Medicines Classification Committee (MCC) agenda item 6.2 – the proposed reclassification from general sale and pharmacy only medicines to restricted medicines for dextromethorphan, opium tincture, squill oxymel and pholcodine.

The reclassification has been prompted by a proposal from Medsafe, who has been alerted to instances of abuse of cough medicines containing dextromethorphan and concern has been raised over the "easy availability of opioid (and opioid-like) cough medicines which can be purchased at a pharmacy or supermarket with healthcare professional supervision." As pholcodine is an opioid this concern for potential abuse has been extended to other cough medicines including pholcodine. Medsafe is requesting the Medicines Classification Committee (MCC) to consider "whether the current classification of cough medicines containing dextromethorphan, opium

tincture, squill oxymel and pholcodine is adequate to manage the risk of abuse and the need for advice on management of cough."

iNova markets a range of OTC and prescription medicines in both New Zealand and Australia. These products include a range of cough medicines containing pholcodine as a single active ingredient and in combination products under the Duro-Tuss and Difflam brands and thus iNova is directly affected by this proposal.

As iNova does not market products containing dextromethorphan, opium tincture or squill oxymel, our submission addresses only the Medsafe reclassification proposal as it relates to pholcodine.

The Medsafe Proposal and Pholcodine

Medsafe proposes to reclassify pholcodine, amongst others, to a restricted medicine on the grounds that this "balances a need for better supervision whilst maintaining access for those who benefit from using these medicines" (Medsafe, 2018, p.1). Two issues were identified in regards to pholcodine in the Medsafe proposal:

- Potential for misuse
- Possible association between pholcodine and anaphylactic reactions to neuromuscular blocking agents (NMBAs) during surgery.

The Medsafe proposal is predominantly concerned with the potential for misuse of dextromethorphan and presents no evidence to support the occurrence of pholcodine misuse or abuse in New Zealand or any other market and acknowledges that "there seems to be a consensus that the addictive potential is low" (p.3); an observation that is inconsistent with the proposed action to make pholcodine a restricted medicine.

Impact on Affected Products

iNova markets the following pholcodine containing products in New Zealand:

- Difflam Anti-inflammatory lozenges with Cough suppressant, Blackcurrant, Sugarfree (benzydamine; cetylpyridium; pholcodine)
- Duro-Tuss Cough Liquid Expectorant Oral Solution 0.8 mg/1 mg per mL (Bromhexine; pholcodine)
- Duro-Tuss Dry Cough Lozenge (Lemon) (cetylpyridium; pholcodine)
- Duro-Tuss Dry Cough Lozenge (Orange) (cetylpyridium; pholcodine)
- Duro-Tuss Dry Cough Liquid Forte Oral Solution, 3 mg/mL (pholcodine)
- Duro-Tuss Dry Cough Liquid Junior Oral Solution, 1mg/mL (pholcodine)
- Duro-Tuss Dry Cough Liquid Regular Oral Solution, 1mg/mL (pholcodine)
- Duro-Tuss Phenylephrine PE Dry Cough + Nasal Decongestant Oral Solution (phenylephrine; pholcodine).

iNova notes that none of these products are mentioned in the Medsafe proposal despite these products having been registered and marketed for up to 30 years. All Duro-Tuss products are pharmacy only medicines. The products are available as both lozenges and oral cough liquids with pholcodine present either as a single active ingredient in some cough liquids or combined with other active ingredients in both lozenge and oral liquid dosage forms. Lozenges contain 5.5 mg pholcodine, whereas the liquid concentration of pholcodine is either 1 mg/mL or 3 mg/mL. In addition, pholcodine has been widely used worldwide since 1950 for the treatment of non-productive cough in children and adults (Blanchard, 2013).

Duro-Tuss is a well-established and well-known brand and is the leading brand of cough medicine

in New Zealand. In 2017 the total cough market in New Zealand was valued at $16.8 million. Duro-Tuss represented [redacted] of these sales and is the market leading cough medicine. Whilst the labeling of these products is not harmonised with Australia [redacted]. Restricting access to Duro-Tuss in New Zealand is likely to result in reduced sales and product volume, which then has an impact on the profitability of the Australian product.

As the market leading brand, reclassifying Duro-Tuss as a restricted medicine would require a significant volume of product to be stored behind the counter and create additional workload for pharmacists. Given the absence of evidence to support the proposition that pholcodine is abused, as acknowledged in the Medsafe proposal, the benefit of reclassification to both public health and the individual patient is dubious and does not outweigh the negative impact on pharmacy management and patient inconvenience that reclassification would cause. As pharmacy only medicines these products already some degree of oversight from a healthcare professional, which helps ensure that the products are safety, effectively and appropriately used.

Pharmacology of Pholcodine

Pholcodine (3-O-(2'-morpholinoethyl)-morphine) is an antitussive without analgesic or addictive properties. Pholcodine is metabolised to the desmorpholinohydroxy metabolite and other metabolites (nor-, nordesmorpholinohydroxy-, hydroxyl-, oxo-, and noroxo-pholcodine). Using GC-MS, unmodified pholcodine can be detected in urine sample 4-7 weeks after ingestion of a single 50 mg dose, the desmorpholinohydroxy metabolite can be detected for 1-2 weeks and the other metabolites only during the first few hours. Morphine can also be detected in urine in the first few days. However it is mainly formed artificially during acid hydrolysis and only in trace amounts by metabolism (Maurer, 1990).

In another study of pholcodine metabolism in three subjects receiving an oral 50 mg dose, pholcodine was found to conjugate with glucuronic acid and 15 % of the pholcodine dose was excreted in urine as the glucuronide and 29% as unconjugated pholcodine. Morphine was detected as a metabolite of pholcodine and 0.5-1% of the pholcodine dose was excreted as morphine glucuronide. (Johansen, 1991). These studies support the assertion by Findlay (1988) that pholcodine is not metabolised to morphine, as only trace amounts of morphine can be detected.
Therapeutic doses of pholcodine have been shown not to cause depression of respiration, CNS excitation or other side effects associated with narcotics. It is thought that the impact of pholcodine is selective on the cough center without affecting the respiratory center. Pholcodine is not euphorigenic, and thus, psychological dependence is unlikely. Clinical trials have not shown any evidence of addiction after prolonged administration of pholcodine (DrugBank, 2018).

As pholcodine is not metabolised to morphine there is no incentive to abuse cough medicines containing pholcodine, as the morphine-induced affects would not be achieved. Therefore if pholcodine were to provide any morphine-like effects, it would be necessary to extract pholcodine from the cough medicine and then attempt conversion to morphine.

iNova has determined that pholcodine is not readily extractable from its formulations and thus there is no incentive for prospective abusers to attempt to misuse our products. It is reasonable to assume that a potential abuser would preferentiality attempt to extract pholcodine from a single active ingredient product with the highest concentration. Generally the easiest path to isolation of an active substance from a preparation is by precipitation from a liquid or selective dissolution from a solid dose. The solubility of pholcodine in water is given as 1:50 assuming neutral pH. If the pH of the solution was increased, by adding sodium hydroxide pellets (readily available as a drain cleaner), pholcodine may precipitate from solution, but references to the solubility of pholcodine at high pH are not readily available.

Alternatively, pholcodine could be extracted into a water immiscible organic solvent such as petroleum spirit (available as a paint thinner or degreaser). With the addition of sodium hydroxide, sufficient mixing and careful separation, followed by evaporation of the organic phase, the pholcodine could be extracted in a fairly high yield.

However, complicating the extraction is the presence in iNova liquid cough medicines of the preservative methyl hydroxybenzoate, which has a similar pKa to pholcodine of 8.4 (ref: *Clarke's*). This means that the yield of the extraction would be a combination of both the pholcodine and methyl hydroxybenzoate in the product because this extraction procedure would probably be as efficient for a hydroxybenzoate as it would be for pholcodine, making it an unsuitable product from which to extract pholcodine.

Other pholcodine containing liquid cough medicines also contain bromhexine, which has a pKa of 9.3 that is almost identical to pholcodine (DrugBank, 2018), so the extraction process described above would probably not separate pholcodine and bromhexine adequately. According to Clarke's (1986), their solubility is similar (1 in 50 in water for pholcodine and 1 in 250 in water for bromhexine) therefore separation based on differential solubility is probably also not practical, since they are already well within their solubility ranges in the product.

A similar situation exists for combination products containing pholcodine and phenylephrine. The addition of another basic drug, phenylephrine, with similar pKas (Clarke's, 1986) of 8.9 and 10.1 respectively complicates extraction. Phenylephrine is much more soluble in water than pholcodine, however since the pholcodine is in solution and well within its solubility limit, it's not clear how pholcodine could be precipitated separately from the phenylephrine. Furthermore, the hydroxybenzoates in these formulations would likely be extracted as well. These factors make these unsuitable products from which to extract pholcodine.

Pholcodine is also available in lozenges, which also contain cetylpyridinium chloride (CPC). The presence of the CPC also complicates extraction. In a pack of 24 lozenges, there is 132 mg of pholcodine, which is less than the pholcodine liquids. CPC is very soluble in chloroform (Clarke's, 1986), so any extraction using a non-polar solvent would recover significant amounts of CPC, along with the pholcodine. CPC and pholcodine also have similar solubility in water of 1 in 20 and 1 in 50 respectively (Clarke's, 1986), hence selective precipitation of the pholcodine seems unlikely. Lower pholcodine per sale unit and the complication of co-extraction of CPC make this product an unsuitable product from which to extract pholcodine.

Thus it is not easy to isolate pholcodine from a product formulation. The abuser would then need to convert pholcodine to morphine, a reaction that involves cleaving an ether bond, which is quite unreactive. Structurally, pholcodine and codeine are quite similar, and converting pholcodine to morphine requires a very similar reaction to converting codeine to morphine. In an article available on the conversion of codeine to morphine (Rice, 1977):, the list of chemicals and equipment cited are well beyond anything available outside of a laboratory supply catalogue, and presumably beyond the skill, equipment and reagents available to a home chemist.

In summary, the chemistry of pholcodine extraction and subsequent conversion to morphine illustrates that pholcodine present in cough medicines is not readily available for misuse or abuse and thus a change to a restricted medicine classification is unwarranted.

Abuse Potential of Pholcodine

The abuse potential for pholcodine is at best tenuous. The available evidence as presented by

Medsafe is no stronger than suggesting there is *potential* for abuse on the grounds that pholcodine is an opioid.

The addiction liability symptoms and withdrawal symptoms of pholcodine have been summarised by Cahen (1961). In one study neither depression nor euphoria were observed in 8 volunteers given a single subcutaneous dose of pholcodine 100 mg. When pholcodine 120 mg was given to 3 patients this caused headache in one patient and vomiting in the other patients. In another study conducted in morphine addicts, pholcodine subcutaneously injected in doses of 50 to 100 mg failed to produce euphoria, myosis, nausea or vomiting. Oral doses of 400 mg in two patients and subcutaneous doses of 400 mg in two others also had no effect.

Six morphine addicts stabilised on doses of between 120 and 300 mg of morphine were abruptly withdrawn and given pholcodine four hours after the abstinence syndrome appeared. They received total doses of 3500 mg and 5200 mg orally distributed over a 40 hour period. No change in the withdrawal symptoms was observed.

The conclusion from these studies was that pholcodine does not produce either physical dependence or addiction and that pholcodine has less addiction liability than codeine.

The Medsafe proposal has also considered the incidence of cases of drug abuse or dependence reported to CARM and the National Poisons Centre. There were no reports for pholcodine and during the period 1 August 2011 to 5 June 2108 there were 2 calls regarding pholcodine that were classified as “abuse” or “intentional”. Medsafe notes that CARM indicated that they would be unlikely to receive reports of drug abuse or misuse and thus reports to CARM cannot reflect the true extent of abuse. If this reasoning is valid then one would also expect to see low reports of other medicines which have a history of abuse.

A search of the Australian TGA DEAN database for reports of drug abuse or dependence pertaining to codeine, pseudoephedrine and pholcodine over the period 1971 to May 2018 was conducted. The results are summarised below.

	Pseudoephedrine (71 medicines)		**Codeine (83 medicines)[1]**		**Pholcodine (24 medicines)**	
	Number of cases	**Cases with a Single suspected medicine**	**Number of cases**	**Cases with a Single suspected medicine**	**Number of cases**	**Cases with a Single suspected medicine**
Total AE reports	607	462	1878	730	185	138
Total Psychiatric reports	196	153	415	197	11	8
Total drug abuse/ dependence reports	3	3	101	61	0	0

[1]Includes both prescription and OTC medicines

The DAEN results indicate that reporting of drug abuse and dependence to regulatory agencies is low as indicated by the reports for codeine and pseudoephedrine. However, it would be reasonable to expect over a 47 year reporting period that there would be at least one case of drug abuse or dependence with pholcodine if such a problem existed. iNova has also received no reports of abuse or misuse.

Internet searches also reveal no evidence of pholcodine abuse, whereas this is a widely discussed topic for both codeine and psuedoephredrine indicating there is a lot more interest and activity with these medicines than with pholcodine.

Anaphylactic Reactions to Neuromuscular Blocking Agents (NMBAs) during Surgery

The Medsafe submission also makes reference to a concern raised by the French Agency for the Safety of Health Products (AFSSAPS) regarding a potential risk that pholcodine may lead to IgE-sensitisation to NMBAs, which could result in anaphylactic reactions during surgery. In 2012 the European Medicines Agency (EMA) published an assessment report on pholcodine, which included a review of the pholcodine-NMBA anaphylaxis hypothesis. The report found that:

"*the evidence in support of an association between pholcodine and NMBS related anaphylaxis is circumstantial, not entirely consistent and does not support the conclusion that there is a significant risk of cross-sensitisation to NMBAs and subsequent development of anaphylaxis during surgery. Further data needs to be generated to clarify the possibility of an association between pholcodine use and NMBA-related anaphylaxis*."

Medsafe acknowledged this finding in their submission and also noted that the Australian TGA shares the opinion of the EMA.

Given the purpose of Medsafe's submission appears to have been initiated in response to" instances of abuse of cough medicines containing dextromethorphan" and other cough medicines having "at least the potential for abuse", it is unclear how this rare side effect of uncertain association to pholcodine is related its potential abuse. Furthermore, the proposed action to reclassify pholcodine and other cough medicines to Restricted Medicines seems an unlikely solution to addressing potential adverse outcomes in surgery.

Conclusion

A review of the available data on the abuse potential of pholcodine provides no evidence that pholcodine is currently misused or abused. Furthermore, the chemistry and pharmacology of pholcodine do not support the proposition that pholcodine has abuse potential. Therefore, the proposal to reschedule pholcodine to a restricted medicine is unjustified. To reclassify pholcodine on the basis of a theoretical consideration is to deny the New Zealand public reasonable access to well-established and well-known brands, which have been used for decades for the symptomatic relief of dry cough and create unnecessary practical problems for pharmacy with respect to storage and increased patient consultation. There is no evident public health benefit to reclassification. The current pharmacy only classification provides an appropriate degree of patient oversight to ensure responsible use of pholcodine. iNova recommends rejection of the proposal to reclassify pholcodine to a restricted medicine and the status quo retained.

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inova pharmaceuticals

PHARMACY GUILD OF NEW ZEALAND

21 September 2018

Medicines Classification Committee Secretary
Medsafe
Wellington

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

Dear Sir/Madam

RE: Agenda for the 61st meeting of the Medicines Classification Committee

Thank you for the opportunity to provide feedback on the agenda for the 61st meeting of the Medicines Classification Committee (MCC), to be held on Thursday 2 November 2018.

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: 5.1.1 Reclassification of modified release paracetamol – objection to the proposed recommendation that modified release paracetamol be reclassified from a pharmacy-only medicine to a restricted medicine.
- Agenda item: 6.1 Melatonin prolonged release 2 mg tablets – proposed reclassification from prescription medicine to prescription except when classification (Circadin, Aspen Pharmacare and Natalie Gauld Ltd)
- Agenda item: 6.2 Dextromethorphan, opium tincture, squill oxymel and pholcodine – proposed reclassification from general sale and pharmacy only medicines to restricted medicines (Medsafe)

Each of these agenda items are discussed below.

Agenda item: 5.1.1 Reclassification of modified release paracetamol – objection to the proposed recommendation that modified release paracetamol be reclassified from a pharmacy-only medicine to a restricted medicine.

The Guild supports the objection on the proposed reclassification of modified release paracetamol from pharmacy-only medicine to restricted medicine.

Previously, we had provided support for the proposed reclassification as a restricted medicine. We initially supported the change in reclassification due to our concerns around therapeutic error and the ability for emergency doctors to manage the toxicity of paracetamol between the modified release and standard formulations.

Currently, modified release paracetamol only accounts for 0.22% of calls recorded by the National Poisons Centre. Taking into account the new information about the

current situation in Denmark and clarity of the overdose protocols used in emergency situations in New Zealand, we now feel comfortable for modified release paracetamol to remain a pharmacy-only medicine.

We support the classification remaining pharmacy-only, provided that a dedicated training programme is implemented to ensure pharmacy staff can provide the necessary education around the different formulations of paracetamol. Pharmacy staff, when suitably trained to provide this information to patients, have clear expectations about when to refer a patient requiring further advice to a pharmacist.

We feel comfortable that our original concern around ensuring appropriate advice is provided, can be addressed through a dedicated training programme for pharmacy staff.

Agenda item: 6.1 Melatonin prolonged release 2 mg tablets – proposed reclassification from prescription medicine to prescription except when classification (Circadin, Aspen Pharmacare and Natalie Gauld Ltd)

The Guild supports the proposal to reclassify melatonin prolonged release 2mg tablets from prescription medicine to prescription except when classification.

We previously opposed the MCC 60th agenda proposal to reclassify melatonin as a dietary supplement. However, we supported the proposal for oral melatonin to be allowed to be purchased under the supervision of a pharmacist.

We support the "prescription-only except when" model as an appropriate mechanism for melatonin to be provided to patients by an accredited pharmacist. This ensures that there is a requirement for a pharmacist to complete an approved training course before they can provide melatonin to patients. This classification prevents the direct importation of melatonin by patients, ensuring patient safety in accessing melatonin through the appropriate channels.

Previous attempts to reclassify melatonin for sale by a pharmacist were not approved on the grounds that there were questions around the suitability of pharmacists to correctly diagnose primary insomnia.

We have previewed the proposed training outline and the screening tool to be used during consultations. The screening tool was developed for use in general practice with additional questions tailored for use during pharmacist consultations. We believe the screening tool is robust and well designed to ensure pharmacists can provide a safe and effective treatment option to their patients. We feel that the screening tool addresses the previous concerns of the MCC around the ability to correctly diagnose primary insomnia and to have a suitable mechanism to refer secondary insomnia.

Agenda item: 6.2 Dextromethorphan, opium tincture, squill oxymel and pholcodine – proposed reclassification from general sale and pharmacy only medicines to restricted medicines (Medsafe)

The Guild supports the proposal to reclassify dextromethorphan, opium tincture and squill oxymel to a restricted medicine.

The pharmacy profession has a professional responsibility when selling any medicines of potential misuse. Under the Pharmacy Council Code of Ethics, a pharmacist "promotes the safe, judicious and efficacious use of medicines, and prevents the supply of unnecessary and/or excessive quantities of medicines, or any product which may cause harm". Pharmacists have a role as medicine gatekeepers, where they must continue to maintain a supply of medicines for legitimate users but also exercise the appropriate supervision to ensure medicines do not end up in the wrong hands.

Best practice recommends that any medicine, regardless of its classification, that is likely to cause or have a potential for misuse should not be accessible to the public for self-selection. These medicines should be stored and displayed in such a way that the pharmacist can exert supervision over their sale. It is commonplace for our members to treat medicines such as Gee's Linctus as a restricted medicine. In a lot of cases Gee's Linctus is already kept behind the counter and out of sight. The sale is often recorded into the pharmacy software in the same manner as any restricted medicine. As it already exists in practice, we feel it is appropriate to reclassify opium tincture and squill oxymel as restricted medicines.

We have significant concerns about the unsupervised sale of any general sale medicine that has the potential for misuse. We feel that it is unacceptable that dextromethorphan can be bought freely by customers without the safe guard of a health professional. Particularly as there is a long history of misuse amongst teenagers and young people, and an even greater concern lies as it may provide a first step towards the misuse of stronger substances. To keep in line with best practice around medicines with the potential for misuse, we feel that it is necessary to reclassify dextromethorphan as a restricted medicine to ensure that appropriate monitoring can be provided by the pharmacist.

We do not support the reclassification of pholcodine to a restricted medicine. We feel that there is insufficient evidence of misuse with pholcodine, and therefore recommend that the classification remains unchanged. However, we do caution the potential for significant IgE sensitisation to neuromuscular blocking agents. We feel that a change in classification to a restricted medicine will be ineffective in helping to manage this concern. Even though this would allow for the recording of sales of pholcodine, there is no current mechanism for this information to be recorded in a centralised shared information platform. Instead, we request that Medsafe conducts further study into the significance of this concern and to determine a more suitable course of action.

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 a.shum@pgnz.org.nz or 04 802 8209.

Yours sincerely,

Nicole Rickman
General Manager – Membership and Professional Services

Pfizer New Zealand
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21 September 2018

Jessica Lo
The Secretariat
Medicines Classification Committee
Medsafe
PO Box 5013
WELLINGTON 6145

Email: committees@moh.govt.nz

Dear Ms Lo

Re: Agenda for the 61st Meeting of the Medicines Classification Committee

Thank you for the opportunity to provide feedback on the agenda for the 61st meeting of the Medicines Classification Committee (MCC). This feedback concerns item 6.2: *Dextromethorphan – the proposed reclassification from general sale and pharmacy-only medicines to restricted medicines*. Pfizer's portfolio does not include the other actives addressed in this proposal and therefore the response is confined to dextromethorphan.

Executive Summary

Dextromethorphan is recognised as a safe and effective oral cough suppressant, and is well tolerated when used as directed. There is extensive marketing and safety experience, having been available for over 50 years and being one of the most widely used cough medicines worldwide. As such, there there is a significant amount of information available on this substance.

The available evidence suggests that abuse of dextromethorphan in New Zealand is limited in prevalence and scope, and not trending upward. The mixed clinical effects of high doses of dextromethorphan include unpleasant symptoms such as dysphoria, nausea, vomiting, blurred vision and disorientation, which would limit its appeal as a preferred substance of abuse. Data also reflects measurable but comparatively low levels of negative health outcomes from reported abuse.

There is insufficient evidence that dextromethorphan is abused on a sufficient scale so as to constitute a public health and social problem warranting a change in scheduling status. Scheduling of medicines should be based on the benefit-risk profile, and the data supports that this remains favourable.

There appears to be no new evidence to support a change to the current scheduling status of dextromethorphan, a position which is consistent with outcomes of previous MCC reviews. Classification as a restricted medicine would unnecessarily limit access for those New Zealand consumers who have a legitimate need to relieve cough and cold symptoms, and would represent unwarranted over-regulation. Available information indicates that there is a low risk of abuse potential with dextromethorphan and such a profile does not justify decreasing consumer access to an effective treatment for cough.

Market History

Dextromethorphan has been marketed as an antitussive agent indicated for cough suppression for over 50 years. It was first approved as an over the counter medicine (OTC) by the Food and Drug Administration (FDA) in 1958[1], whilst the European Union Reference Date is 1 January 1966. Pfizer received first regulatory approval for dextromethorphan on 18 December 1985 in Ireland. Complete cumulative patient exposure to dextromethorphan from marketing experience since the International birth date is not available. However, during the 12 year period 2003 to 2015, it is estimated that **1,099,392,033** standard units of dextromethorphan have been distributed globally (Appendix A). A more recent review estimates that in a single 12 month period (2 November 2016 through to 1 November 2017) worldwide exposure was in excess of 45 million standard units (Appendix C).

Of the active ingredients used to relieve cough, dextromethorphan is the most widely used. In the US, dextromethorphan-containing OTC medicines account for 85-90% of all medicines containing a cough suppressant[2].

Dextromethorphan is approved and is currently marketed in 26 countries worldwide. It is widely available as a non-prescription medicine and countries include the vast majority of European countries, United States (including general sale access), Canada (including limited general sale access), Japan, Australia and New Zealand.

In New Zealand, Pfizer markets liquid and solid dose format dextromethorphan-containing products. A small number are classified as general sale. The majority are classified as pharmacy-only medicines, all of which have labels that are harmonised with Australia, enabling the same product to be marketed in both countries. Any amendment to scheduling resulting in increased disparity between Australia and New Zealand would have a significant impact on cost of goods and would place at risk the feasibility of maintaining supply.

Pharmacology & Toxicology

Dextromethorphan, the d-isomer of levomethorphan, is a non-narcotic, non-addictive cough suppressant. It acts on the cough centre in the medulla oblongata by elevating the threshold for coughing (Appendix A).

Dextromethorphan has no structural similarity to levorotary morphine derivatives. On this point, the Medsafe proposal to the MCC provides a contradictory assessment as to whether dextromethorphan is an opiate. Dextromethorphan does not act as an opioid receptor agonist and it lacks any morphine like effects[3]; to suggest otherwise is inappropriate and inaccurate. Furthermore, whilst codeine and other opiates are used for pain, dextromethorphan is devoid of analgesic activity, and used only for treating cough, a self-limiting condition.

There are no signals of illicit diversion of dextromethorphan, or conversion into a controlled substance, an observation that is not surprising given its chemical structure and actions described above.

General Safety and Efficacy Considerations

Dextromethorphan is recognised as a safe and effective oral cough suppressant, and is well tolerated when used as directed. There is extensive marketing and safety experience, having been available for over 5 decades and being one of the most widely used cough medicines worldwide.[1]

At recommended doses, dextromethorphan has a good safety and efficacy profile, with no effect on respiration, the cardiovascular system, the gastrointestinal tract, or mucociliary activity. Also, it has little or no sedative and analgesic effects.[4-6]

Acute cough is highly prevalent in the general population and multiple studies have demonstrated that the majority of consumers around the world self-medicate for cough and the common cold[7]. The UK's National Institute of Clinical Excellence (NICE) recognises that dextromethorphan has a role to play in the self-care of viral cough and is recommended in order to decrease antibiotic use.[8]

Whilst usually minor in nature, effective relief from cough is important given its prevalence and the negative and potentially significant impact on individuals and their daily routines, including sleep and presenteeism. Its safety and efficacy is well recognised including by regulators such as the Therapeutic Goods Administration (TGA) in Australia which has included it in an OTC Medicine Monograph.

Self-selection access to non-prescription medicines enables New Zealand consumers to take appropriate control of their own healthcare and have suitable access to treatments to manage minor conditions. In the pharmacy setting, the pharmacist is available, accessible and approachable to provide advice if needed.

Abuse and Dependence Potential

The maximum therapeutic dose of dextromethorphan to treat cough is 30mg for adults and children over 12 years of age. The psychoactive effects are observed at doses far exceeding the therapeutic doses. These range from mild stimulation at doses 3-7 times the therapeutic dose through to visual distortion, loss of motor coordination and sedation at doses 10-50 times the therapeutic dose[9-11]. As a result, abuse of dextromethorphan is likely to lead to undesirable physical effects. Higher doses of dextromethorphan that provide a sense of feeling drunk or high are also frequently associated with additional unpleasant symptoms of dysphoria, nausea, and vomiting.

Clinical studies report that, at high doses (8-20 times the maximum therapeutic dose), dextromethorphan can exert mixed clinical effects, eliciting both euphoria and dysphoria. These effects are often associated with nausea and vomiting, as well as "disliking" sensations in abuse liability evaluations. Dysphoria and "disliking" increase in a dose-dependent manner[1]. These clinical findings are consistent with qualitative research among substance abusers which shows little recurring abuse of dextromethorphan[2].

The mixed clinical effects associated with high doses of dextromethorphan are a key consideration given such a profile would limit its appeal as a preferred substance of abuse. Furthermore, consumption of such high levels from solid dose formats, or liquids (which contain sorbitol) is difficult to achieve and reduce the likelihood of repeat and excessive use.

In the misuse and abuse of dextromethorphan, withdrawal or tolerance does not appear to be a factor. There is limited evidence in the literature that dextromethorphan produces physical dependence as measured by tolerance or withdrawal. Isolated case reports do however suggest it may produce psychological dependence[3].

In 2012, the WHO Expert Committee on Drug Dependence (ECDD) determined that dextromethorphan was a medically useful active, with a relatively low abuse liability, following their comprehensive review of its convertibility, toxicology and dependence and abuse potential. It was concluded no additional controls were required.

Overall, the abuse and dependence potential of dextromethorphan is low.

Prevalence of Abuse and Outcomes Data

The evidence included in Medsafe's submission (CARM database and National Poisons Centre data) indicates reports of abuse of dextromethorphan are infrequent and isolated. The submission contains

no information to suggest a new emerging public health problem associated with the abuse of dextromethorphan-containing products.

[redacted]

The cough cold category in New Zealand is seasonal in nature, and is variable depending on the severity of each particular season. [redacted]

Medsafe's submission asserts that dextromethorphan may "*encourage initiation and progression of substance abuse in teenagers……..DXM may entice young users to experience broader and illicit substance abuse experiences*" without provision of any supporting evidence. Survey data from the United States suggests the opposite may be the case with results indicating abusers are already engaged in substance abuse behaviours[12].

Overall, the numbers of reports of dextromethorphan abuse in New Zealand appear to be very low irrespective of the dataset examined. The data suggests that the issue is limited in prevalence and scope, and not trending upward. There is inadequte evidence that dextromethorphan is abused on a sufficient scale in New Zealand so as to constitute a public health and social problem warranting a change in scheduling status.

[redacted]

As dextromethorphan has been widely used over the last 50+ years, there is extensive experience with this ingredient. Whilst there have been isolated reports of abuse during this time, it has largely been observed in teenagers and young adults[3]. Databases which examine outcomes or

consequences, including substance abuse treatment admissions, accident and emergency department visits for non-medical use of dextromethorphan, or abuse-related adverse event terms, reflect measurable but comparatively low levels of negative health outcomes from reported abuse. They also provide further support to the findings on the pattern and reported level of abuse that teens and young adults who abuse non-prescription cough products appear to discontinue such abuse in adulthood[2].

The National Poison Data System (NPDS) captures data on reports (calls and online) to US poison centres involving dextromethorphan abuse. A group of researchers utilised this dataset to examine dextromethorphan abuse trends for the period 2000-2015[13]. Overall, the annual rate of dextromethorphan intentional abuse calls increased three-fold between 2000 and 2006 and subsequently plateaued from 2006 to 2015. Over the same 2006-2015 period, in adolescents aged 14-17 years, the rate for dextromethorphan abuse calls decreased by 56.3%. Rates of abuse in adults were observed to be much lower than in adolescents, whilst the rates of abuse in adults aged 22-29 increased steadily[13]. To the extent there is local abuse, USA survey data indicates abusers are already engaged in substance abuse behaviours[12].

Conclusion

Together, the data shows that the abuse and dependence potential of dextromethorphan is very low. While there is abuse or attempts to abuse medicines containing dextromethorphan, the overall prevalence of abuse is comparatively low relative to other substances. International data suggests abuse appears to be concentrated among teens and young adults, particularly those with histories of alcohol, marijuana and/or tobacco use. Non-medical use and abuse outside of these populations appears to be rare. Based on the available safety and efficacy data for dextromethorphan, the overall benefit-risk profile is favourable.

The benefits of dextromethorphan must be considered when assessing public health risks. Given that relatively large amounts of dextromethorphan-containing cough medicines are sold annually in New Zealand, and that many consumers use these medicines to relieve cough, any burden to public health as a result of level abuse is outweighed by the health benefits of these medicines.

Reclassification of dextromethorphan as a restricted medicine would have a potential negative public health impact by limiting access for those New Zealand consumers who have a legitimate need to relieve cough and cold symptoms.

In conclusion, there is no evidence to suggest any change in the benefit-risk profile of dextromethorphan, and therefore any change to the current scheduling in New Zealand is unwarranted.

Yours sincerely

[redacted]

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21 September 2018 MT18-498

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Dear Jessica,

Agenda for the 61st meeting of the Medicines Classification Committee

Thank you for giving The Royal New Zealand College of General Practitioners the opportunity to comment on the Agenda for the 61st meeting of the Medicines Classification Committee.

Introduction to general practice and the College

General practice is the medical specialty that treats patients: with the widest variety of conditions; with the greatest range of severity (from minor to terminal); from the earliest presentation to the end; and with the most inseparable intertwining of the biomedical and the psychosocial. General practitioners (GPs) treat patients of all ages, from neonates to elderly, across the course of their lives.

GPs comprise almost 40 percent of New Zealand's specialist workforce and their professional body, The Royal New Zealand College of General Practitioners (the College), is the largest medical college in the country. The College provides training and ongoing professional development for GPs and rural hospital generalists and sets standards for general practice. The College has a commitment to embed the three principles (participation, partnership and protection) of Te Tiriti o Waitangi (Treaty of Waitangi) across its work, and to achieving health equity in New Zealand.

Health equity is the absence of avoidable or remediable differences in health outcomes and access to health services among groups of people, whether those groups are defined socially, economically, demographically, or geographically (WHO). To achieve health equity, we advocate for:

- A greater focus on the social determinants of health (including labour, welfare, education, housing, and the environment).
- Funding and support to sustain the development of a GP workforce of sufficient capacity to meet population need for access to quality primary medical care, particularly in rural and high need areas.
- Sustained focus on measures to reduce smoking and to increase healthy food options for low-income families.
- Improved integration of primary, community, and secondary care health and social services which ensures the provision of high-quality services.
- Universally accessible free primary health care for children and low-income families, because health inequities begin early and compound over the life course.
- A review of the funding model for primary care to ensure that resourcing is allocated equitably across diverse populations with differing needs.

Submission

The College wishes to comment on the following three agenda items.

- 5.3 Melatonin - proposed reclassification from prescription medicine to a restricted medicine
- 6.1 Melatonin prolonged release 2 mg tablets – proposed reclassification from prescription medicine to prescription except when classification
- 6.2 Cough medicines

The two agenda items concerning Melatonin will be considered together

Agenda items 5.3 and 6.1

The College supports increasing access to melatonin. The issue before the Committee is which of the two proposed regulatory classifications will best achieve this. The NZMA submission on this topic outlines the issue well and we have included it below with their permission.

> Items 5.3 and 6.1 (reclassification of melatonin) We note that the 61st meeting of the MCC will consider two separate agenda items regarding the reclassification of melatonin. Item 5.3 relates to the proposed reclassification of oral melatonin in doses of 3mg or less from prescription medicine to restricted medicine. Item 6.1 relates to the proposed reclassification from prescription medicine to prescription except when provided at a strength of 2mg prolonged release to people who meet clinical and eligibility criteria when sold by a pharmacist who has completed an approved training programme. We are supportive of a regulatory framework that supports better access to melatonin (including taking into account cost to patients) while ensuring appropriate use (particular concerns relate to the long-term use of melatonin and of parents medicating children) and safeguarding standards of safety, efficacy and quality (including good manufacturing process). A reclassification from prescription medicine to prescription except when provided at a strength of 2mg prolonged release to people who meet clinical and eligibility criteria when sold by a pharmacist who has completed an approved training programme should address concerns about inappropriate use and may also improve access for some patients. However, the cost of a pharmacist consultation is likely to represent a significant barrier for many people. While a reclassification of melatonin from prescription to restricted medicine could be expected to improve access and cost (no pharmacist / GP consultation fee), it could widen inappropriate use even though it provides for some monitoring of patterns of purchase. Furthermore, our understanding is that if a medicine is changed to restricted (pharmacist-only) status, it would potentially allow importation of unregulated melatonin from overseas with all the attendant concerns about poor quality and lack of oversight. We recommend that the committee balance all these factors when determining which regulatory option is best for melatonin[1].

In addition to supporting the NZMA stance we would like to make the following points.

The proposal outlined under agenda item 6.1 (a prescription except classification) would see pharmacists undertaking additional training in sleep disorders, including training to advise on non-pharmacological management. It will also lead to the increased availability of educational material for patients. This will benefit patients and a further benefit will be that some patients with secondary insomnia who would not otherwise consult a doctor will be identified by the pharmacist and encouraged to seek assistance.

[1] http://www.nzma.org.nz/__data/assets/pdf_file/0004/84784/NZMA-Submission-on-agenda-of-61st-meeting-of-the-Medicines-Classification-Committee.pdf

As mentioned in the NZMA submission the prescription-except option (item 6.1) would continue the restriction on the purchase of melatonin from overseas. If melatonin instead became a restricted medicine, the combination of the ease with which unregulated melatonin could then be purchased from overseas, and the frequency of sleep problems in children will probably lead to the inappropriate use of melatonin in children. A prescription-except classification as proposed in item 6.1 would retain the prohibition on purchase from overseas, while increasing access to melatonin for those indications for which Circadin is licenced and for which there is evidence of safety and effectiveness.

The proposal under item 6.1 would not enable pharmacists to supply Melatonin for the unapproved indications for which some people use melatonin currently, for example to manage jet lag. The only legal mechanism for supply for an unapproved indication is under section 25 of the Medicines Act. Unlike pharmacists GPs can prescribe medicines for unapproved indications under section 25. The GP must however take the responsibility for the safety of prescribing for such off-label use. [2]

The fact that an application has not been made to add such indications, suggests that the evidence of safety and effectiveness to support such an application is not available. If evidence for additional indications becomes available and these are added to the license this would open a pathway that could lead to appropriately trained pharmacists being able to supply melatonin in such circumstances.

Finally, we received feedback from members who would be keen to see PHARMAC fund 2mg slow release melatonin as an alternative to the funded but addictive hypnotics such as benzodiazepines and zopiclone.

Agenda item 6.2 Dextromethorphan, opium tincture, squill oxymel and pholcodine – proposed reclassification from general sale and pharmacy only medicines to restricted medicines

The College supports this Medsafe initiated reclassification proposal as it will decrease the ease with which these medications can be abused. Although cough medicines are popular with patients a 2014 Cochrane review found no good evidence for or against the effectiveness of OTC medications in acute cough[3]. Removing them from the open shelves of pharmacies to where they can only be purchased after discussion with the pharmacist will enable the pharmacist to suggest alternative management of cough where appropriate.

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

Michael Thorn
General Manager – Strategic Policy

[2] https://bpac.org.nz/BPJ/2013/March/unapproved-medicines.aspx

[3] https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001831.pub5/abstract

SMI
New Zealand
Self-Medication Industry
Association Inc.

September 20th, 2018

The Secretary
Medicines Classification Committee
Ministry of Health

Email: committees@moh.govt.nz

Dear Sir or Madam

We wish to make submissions to the 61st Meeting of the Medicines Classification Committee on:

- Item 5.1.1 Reclassification of modified release paracetamol
- Item 6.1 Melatonin prolonged release 2 mg tablets, and
- Item 6.2 Proposed reclassification from General Sale of dextromethorphan, opium tincture and squill oxymel.

NZSMI (New Zealand Self Medication Industry Association) is the peak body representing companies involved in the manufacture and distribution of consumer health care products (non-prescription) in New Zealand. NZSMI also represents related businesses providing support services to manufacturers, importers and distributors including advertising, public relations, legal, statistical and regulatory advice.

As this industry representative, NZSMI is a key stakeholder in scheduling matters and we appreciate the opportunity, on behalf of our membership, to have our comments form part of the deliberations around these issues. Please contact me should you require any further clarification relating to this commentary.

Yours sincerely

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NZSMI

Submission to Medicines Classification Committee
61st Meeting

Agenda Item 5.1.1: Reclassification of modified release paracetamol – objection to the proposed recommendation that MR paracetamol be reclassified to a restricted medicine

Introduction

1. The New Zealand Self Medication Industry Association (**NZSMI**) represents the importer, manufacturers and distributors of the bulk (80%) of New Zealand's over the counter (**OTC**) product sales in pharmacy, grocery and complementary healthcare outlets. It exists to promote the responsible use of self-medication products. It works closely with Medsafe and other industry bodies to improve the outcomes of the New Zealand health strategy and in particular, the safe and cost-effective use of medicinal products.

Comment

2. NZSMI submitted to the MCC meeting of 26 April 2018 on behalf of its members and did not support the Medsafe recommendation to up-schedule.

3. NZSMI acknowledges the decision of the MCC to suggest that modified release paracetamol (**MR paracetamol**) be pharmacist only. However, we believe that a renewed analysis of the New Zealand specific data and the availability of deeper global analysis of paracetamol use and misuse warrants reconsideration of this decision.

4. The decision to suspend MR paracetamol products in Europe centred around overdose issues raised by a small number of European countries, particularly Sweden. The Swedish report was subsequently reviewed by the Pharmaco Vigilance Risk Assessment Committee (**PRAC**) and subsequently 19 out of the 33 EU member states entitled to vote, then voted in favour of the decision to up-schedule (a slim majority).

5. The major thrust of the PRAC report centred around procedures developed for paracetamol overuse, misuse and abuse. It is important to note that the procedures in Sweden where the problem primarily arose are different to those used in New Zealand and NZSMI contends that this point did not receive adequate weighting by the MCC.

6. It is important to note that the overdose guidelines for MR paracetamol as it exists in New Zealand have been in place since it was first launched in the market in 2008. The overdose treatment protocol is based on dose principle and is different to that used in Sweden. It is important to note these substantial differences are based on the patient's blood of paracetamol, whereas the New Zealand guidelines are based on the dose level of paracetamol, regardless of whether the dose was via modified release or immediate release paracetamol. This fundamental difference would appear to be the reason that paracetamol overdose is treated more successfully in New Zealand than in those countries adopting the blood level guidelines.

7. NZSMI agrees with the MCC mandate that New Zealanders should have safe proven effective medications appropriately available with the emphasis on 'safe'. The safe use of MR paracetamol is promoted by specialist advice coming from a GP or pharmacist and the

availability of detailed appropriate information in the form of packaging, patient leaflets and other media, including websites and online advice.

8. There are tens of millions of doses of paracetamol purchased and prescribed in New Zealand annually. It is unfortunate that paracetamol is often used by those wishing to self-harm and NZSMI acknowledges paracetamol toxicity in abuse situations is dangerous. It is important to note that the level of implication of MR paracetamol in cases of intentional abuse and misuse is extremely low. We are aware that a single member of NZSMI (GSKCH or Glaxo Smith Kline Consumer Healthcare) have provided detailed information to the MCC on the incidents rates of overdose with MR paracetamol comparing rates in New Zealand, Denmark and Sweden. We see no benefit in duplicating this information but would ask that the MCC give due cognisance to this data, which again highlights the market differences between these selected European countries and New Zealand.

9. Also worth noting is that the prescription only status of MR paracetamol in Sweden has not resulted in a lower incidents rate of overdose than we have in New Zealand – the incidents in Sweden being four times greater than New Zealand. This would lead one to conclude that changing the scheduling is not a panacea for the risk of danger caused by MR paracetamol.

10. The argument for up-scheduling has centred primarily around possible confusion that New Zealand consumers may take MR paracetamol assuming it to be the far more common instant release paracetamol. NZSMI suggests this is a weak argument given the substantial price difference between the two variants, the substantially different wording and packaging presentations and the considerable difference in the way the product is represented on pharmacy shelves. In terms of shelf facings within an analgesic area MR Paracetamol occupies a very small percentage of overall space as facings represent market demand and this product has a small but important market demand.

11. Since our submission to the 60th meeting of the MCC, information has been received from the Danish Medicines Agency that they have lifted the product licence suspension and sale of MR paracetamol (this occurred in mid-May 2018). It is important to note that unlike Sweden, the Danish regulator has overdose treatment protocols based on the dosage principle rather than the blood level principle, which exists in Sweden. It is our contention that the Danish authorities have reviewed their position based on reanalysis of existing data and we suggest it is appropriate that the MCC also consider re-evaluation.

12. The primary mandate of the NZSMI is to encourage the appropriate availability of safe proven and effective self-medications. The very fact that the MCC has considered the regulatory status of MR paracetamol has made it a discussion point within the industry. NZSMI membership includes the Pharmaceutical Society, Pharmacy Guild and Green Cross Health who have strong influence, communication and connection with all New Zealand pharmacy. Even if the regulatory status of MR paracetamol is retained as pharmacy only, where we believe it is most appropriate, there will be discussion about improved patient care, advice, appropriateness and safety when considering the marketing and supply of all types of paracetamol whether it be in combination, immediate release or modified release. This is part of the daily change process of any industry and particularly the pharmacy industry.

13. NZSMI suggests that the MCC should retain the current regulatory status of MR paracetamol as pharmacy only, but should suggest to the industry that further education and awareness programmes are appropriate for general practioners, general practitioner staff, Emergency Room doctors, pharmacists and pharmacy staff. These measures would

highlight the special nature of this valuable tool within the self-care arsenal and also highlight the need for vigilance around its appropriate use. NZSMI is keen to work with all stakeholders to ensure these improved measures are delivered to the industry and the public.

NZSMI SUBMISSION
TO THE 61st MEDICINES CLASSIFICATION COMMITTEE MEETING
REGARDING RECLASSIFICATION OF COUGH MEDICINES

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. The major manufacturers who have products registered with these ingredients are members of NZSMI.

Summary

1. The NZSMI position on the proposed reclassification of cough medicines containing dextromethorphan, opium tincture, squill oxymel and Pholcodine to restricted medicines is:

    1.1 The majority of people who use OTC cough medicines do so responsibly.

    1.2 Consumer safety is the primary concern of NZSMI and its members. This Medsafe submission does not provide a balanced view of the risks and benefits of these ingredients and does not provide sufficient explanation or evidence to warrant increased restricted access.

    1.3 The reason given for the proposal by Medsafe is that "because of the recent look at codeine containing cough and cold products, it was reasonable to look at other cough and cold products". To conflate the codeine containing cough/cold products with cough preparations containing these ingredients is confusing and potentially misleading, particularly as codeine has a strong analgesic profile (which none of these have) and defined opioid characteristics.

    1.4 The easy availability of cough relief is important to reduce personal disruption and discomfort and to reduce spread of bacterial and viral infection. The New Zealand Health Strategy has a goal, under the heading "Closer to Home" : "People have access to services, information and support as close to home as possible. These services are available when they want them, and access is as easy as possible"

    1.5 We do not agree that "Dextromethorphan has a history of abuse in New Zealand" (Page 1,Para 2) is a reasonable statement and the Medsafe paper shows only isolated cases of misuse are recorded.

    1.6 We can find no local or international research data that agrees with the statement "DXM is an opioid" as stated in the Medsafe paper under Background and find it confusing that this statement comes after the earlier statement "Dextromethorphan is a substance that does not belong to the opioid family

1.7 There will be potential negative consequences to making OTC cough medicines containing these ingredients pharmacist only. These include delay in seeking treatment due to restricted availability and potential additional pressure on GPs and medical centres, many of whom are currently experiencing long waiting times.

1.8 Changing schedules that put New Zealand out of step with Australian regulations means, in most cases, label harmonisation will no longer exist.

1.9 Products containing dextromethorphan (DXM) and Pholcodine are widely available over the counter in many other countries.

1.10 DXM abuse in the United States was a serious issue some years ago and has been mitigated by educational programmes and improved labelling – not up scheduling.

1.11 There is little evidence of an abuse problem in New Zealand apart from low numbers of isolated instances and even if there was a quantifiable problem NZSMI believes that changing the schedule is not a balanced solution in the best interests of improving primary care for New Zealanders.

1.12 There will always be a minute population of any society that will seek mind altering substances by way of abuse and excess and NZSMI contends there are better ways of reducing this than blanket barriers to access; and agrees with the comment in the Medsafe proposal paper that "…other medicines may be misused instead or purchase directed to internet outlets"

1.13 We can find no evidence of abuse of Pholcodine containing products in New Zealand.

1.14 Squill Oxymel is a traditional medicine with anti-inflammatory, anti-oxidant and anti-cholinergic effects used in the treatment of upper respiratory tract inflammation and congestion. It is widely accepted that there are unpleasant and potentially harmful side effects of excessive dosing of Squill but dose guidelines in New Zealand have ensured that this has not manifested itself as a problem, particularly as it is only widely used in combination. It is not an opium derivative and we can find no evidence of abuse or any other reason why it should be restricted to sale by a pharmacist.

1.15 NZSMI notes that Linctus Gee is currently a Pharmacy Only medicine which, in most pharmacies, is treated as a quasi-Pharmacist Only supply.

1.16 NZSMI notes the suggested link causing sensitisation to neuro muscular blocking agents and Pholcodine use. There is conflicting evidence available, over the last twenty years, regarding this hypothesis but enough to raise concern. NZSMI contends that changing the availability of Pholcodine to Pharmacist Only will do nothing to solve this problem if it does exist and the pharmaceutical industry and pharmacy need to work with anaesthetists to improve public education and pre-anaesthesia screening protocols.

1.17 This Medsafe paper highlights the issue that medicine use and abuse reporting data in New Zealand may be inadequate. NZSMI would like to work with Medsafe, CARM and the National poisons centre to change this.

2. Use of Dextromethorphan in other Countries

Dextromethorphan is widely used, and has been for decades in over-the-counter (OTC) settings. It was first approved as a prescription antitussive drug in the United States of America (USA) in 1954 and subsequently as an over-the-counter (OTC) medication in 1958.

Dextromethorphan is currently marketed without a prescription in a wide number of countries:

Non-prescription countries		Prescription countries
Austria	Lithuania	Argentina
Australia	Mexico	Bulgaria
Belgium	Netherland	Chile
Brazil	New Zealand	Denmark
Canada	Peru	France
China	Philippines	Greece
Columbia	Poland	Russia
Croatia	Portugal	South Korea
Czech Republic	Singapore	Turkey
Ecuador	Slovakia Republic	
Finland	Slovenia	
Germany	Spain	
Hungary	Switzerland	
India	Taiwan	
Indonesia	Thailand	
Ireland	United Kingdom	
Italy	USA	
Japan	Venezuela	

Source: Association of the European Self-Medication Industry (AESGP) database and outcome of an internal survey performed in July 2017.

NZSMI is aware that a small number of Health Authorities have taken local decisions regarding the supply status of dextromethorphan containing products due to recreational abuse concerns:

France

In July 2017, French Health Authorities decided a switch back of dextromethorphan products as well as products containing codeine, ethylmorphine and noscapin. This measure was taken to minimize the risk of abuse for recreational purpose in adolescents and young adults and triggered by severe cases (including 2 fatal outcomes in 2017) occurred in France with codeine products.

Czech Republic

Czech Republic Health Authority decided on 15 August 2017 the immediate switch back of all dextromethorphan single INN products in solid forms and requested for other dextromethorphan products to provide a rationale regarding supply status

Further to the assessment of all Companies' feedbacks, Czech Republic Health Authorities decided to maintain these products with a non-prescription status with reinforcing the Risk Minimisation Measures through a direct healthcare professional communication and a close monitoring of abuse cases.

United States
Dextromethorphan abuse concern was also discussed in the US for several years where a risk mitigation plan led by the US Consumer Healthcare Product Association has been effectively implemented.

In all these cases the situations are entirely different to those which exists in New Zealand. After a recent analysis of all available data, NZSMI confirms its position that dextromethorphan containing products should be available with an over-the-counter status, as it has a good efficacy and safety profile, particularly when compared with other non-prescription alternatives.

Oral dextromethorphan 30 mg is the only active substance demonstrating significant suppression of acute cough in clinical trials using objective measures (*Morice et al. 2016*).

Based on its good safety and efficacy profile, and in the absence of any data that demonstrates a prolonged or significant misuse profile in New Zealand over decades NZSMI believes that the current scheduling of dextromethorphan in New Zealand does not need to be reclassified.

3. Consultation with sister organisations Globally

NZSMI has consulted with numerous equivalent organisations in Australia, USA, South Africa, Europe and the UK. NZSMI also consulted with WSMI (World Self Medication Industry Association) with whom it is a member.

WSMI is a Non- Governmental Organization (NGO) in official relations with the World Health Organization since 1977. For these reasons, NZSMI have an interest via WSMI in the WHO Expert Committee on Drug Dependence pre-review of dextromethorphan which occurred in 2012. The Executive summary of that involvement is reproduced as follows;

Dextromethorphan is a safe, effective cough suppressant that has a long history of therapeutic use without a prescription in a wide number of countries around the world. Medicines with the ingredient are among the most widely used cough and cold medicines in the world. Its use dates back more than 50 years.
Data suggest that abuse of dextromethorphan is limited in prevalence and scope, is not trending upward, and is within an identifiable population (largely North American teens). The physical effects from abusing dextromethorphan are generally not desirable, with negative effects of exposure to high doses of dextromethorphan including dysphoria, nausea, vomiting, blurred vision, and disorientation. To the extent there is local abuse, USA survey data indicates abusers are already engaged in substance abuse behaviors. Further, we believe more targeted, effective, and less disruptive interventions than scheduling exist that can address this abuse where it is occurring.
Scientific research on the abuse or dependence potential and prevalence of abuse seen with dextromethorphan support the conclusion that this medication does not merit the types of controls mandated in the UN Convention on Psychotropic Substances. <u>There is insufficient evidence that dextromethorphan is abused on a sufficient scale so as to constitute a public health and social problem warranting the placement of dextromethorphan under international control; nor does dextromethorphan have dependence-producing capacity as is required for scheduling under the Convention on Psychotropic Substances.</u>
The international control of dextromethorphan would result in a reduction in the legitimate use of this safe and effective medication that has benefits that far outweigh its risks. This reduction would come at a great cost to citizens worldwide who benefit from this medicine used without a prescription to

treat their coughs. There is also the potential for an increased burden being transferred to health systems as individuals turn to their physicians for support and to seek a prescription. International control would also raise the potential consequence of additional codeine, dihydrocodeine, or hydrocodone use as cough suppressants, which would come with its own set of negative, unwanted effects.
WSMI encourages the WHO Expert Committee on Drug Dependence to conclude that dextromethorphan should not move forward for further action after pre-review.

It is important to note that WHO agreed with this position and DXM was not recommended for further international supply controls.

The US industry was already responding by this time with a program to raise awareness of the teen abuse issues around DXM with an education program as mentioned in the Medsafe proposal that is credited with 35% reduction by 2015 of abuse by 12 to 17 year olds.

4. Harmonisation of Labelling.

While it is accepted that the MCC has no specific concern about the commercial effects of its' regulatory recommendations, NZSMI believes it is important to be aware of the impact on access to primary care of changing the scheduling of certain classes of products.

Linctus Gee is not marketed in Australia but Pholcodine and Dextromethorphan are available as Pharmacy Only medicines in several different dosage forms. Most these lines have harmonised labels, allowing the same product in the same box to be marketed in both countries thus achieving an economy of scale. If these items are up scheduled in New Zealand to Pharmacist Only this harmonisation will no longer exist and separate packaging and labelling for the New Zealand product will be required.

Commercially, this will seriously threaten the viability of these products as the New Zealand market is small and the costs of regulation, marketing and distribution are high in a very competitive market. The upshot could well be that the Pharmacist has NO Pharmacist Only product to supply or that prices to the consumer rise to such an extent to cover cost that many are disadvantaged.

Many scoff at this suggestion citing global pharma profits seem universally high. This is dangerous thinking as large multi-nationals are in ever increasing fierce competition that is driving margins down and many are beginning to think that even a combined Australia/New Zealand market is not substantial enough to warrant sustained investment.

NZSMI stands by its warrant to promote the appropriate availability of safe, proven, quality OTC medicines and believes a global perspective is necessary, alongside cognizance of local nuances like the very low level of abuse of cough control preparations containing DXM and Pholcodine, when considering scheduling changes.

5. Current practices around the sale of Linctus Gee

We can find no formal data that an abuse problem exists in New Zealand with this product and pharmacists regard it as a useful tool in the control of acute common cold, mucous and respiratory distress.

However, New Zealand pharmacists are acutely aware of the potential risks surrounding the sale of an opiate derivative containing medicine.

While linctus Gee is currently scheduled as Pharmacy Only most retail outlets display this product with empty boxes on shelf. This is a time proven “half-way house of self-regulation versus formal regulation”. It requires the customer to seek help from pharmacy staff to retrieve stock from behind the counter. It gives pharmacy counter staff the opportunity to evaluate the appropriateness of the sale via questioning and observation and refer to a pharmacist if required.

6. General Sale and Pharmacy Only Supply

NZSMI supports the current scheduling of DXM in New Zealand as there is no evidence to support a change in classification is warranted.

NZSMI also wishes to highlight the difference between GSL and Pharmacy Only from a practical point of view. Pharmacy Only Medicines are almost always presented for sale close to the dispensary in New Zealand pharmacies. Most New Zealand pharmacies have staff with specific training in OTC medicinals and many larger pharmacies have specialized staff dealing only in OTC medicinals and complimentary health care. This training is provided by the Pharmaceutical Society, the Pharmacy Guild, Green Cross Health and other pharmacy groups, NZSMI supplier members and is also available in continuing education on-line courses.

Pharmacy staff monitor patient requests for medication and use their training to recommend appropriate treatment to add value to the sale and relationship that is “Pharmacy”. They are also aware of the health risks and industry reputational risk of excessive supply. As such, staff will regularly check with management (often, but not always, a pharmacist) or the duty pharmacist if there are concerns. NZSMI acknowledges that these comments are anecdotal and have no research supporting them. It is currently investigating how formal research might be conducted to quantify the level of support and intervention provided by pharmacists and pharmacy staff.

NZSMI maintains informal intervention exists at “Pharmacy Only” supply level to help prevent excessive sale, misuse and abuse and that Pharmacist Only restrictions are not indicated and amount to over-regulation for the group of ingredients under discussion.

NZSMI

Submission to Medicines Classification Committee
61st Meeting

Agenda Item 6.1: Melatonin prolonged release 2mg tablets – proposed reclassification from prescription medicine to prescription except when classification

Introduction

1. The New Zealand Self Medication Industry Association (**NZSMI**) represents the importers, manufacturers and distributors of the bulk (80%) of New Zealand's over the counter (**OTC**) product sales in pharmacy, grocery and complementary healthcare outlets. It exists to promote the responsible use of self-medication products. It works closely with Medsafe and other industry bodies to improve the outcomes of the New Zealand health strategy and in particular, the safe and cost-effective use of medicinal products.

Comment

2. NZSMI supports the application seeking reclassification of melatonin from prescription medicine to "prescription medicine except when".

3. NZSMI does not, currently, support any further changes to the availability of melatonin of any strength and in particular, feels it is not currently appropriate that this product should be pharmacy only.

4. Although melatonin is widely available and can be obtained from the United States, it is a more highly restricted medicine in most other countries, including the UK and Australia. The dietary supplementary status in the US is not something NZSMI believes should be duplicated in New Zealand.

5. NZSMI is concerned about the quality of product coming into New Zealand and there have been numerous instances of attempts to import unregistered medicines in New Zealand. This issue has been highlighted by the recall of unapproved melatonin products in recent years in New Zealand. We believe that these risks can be mitigated through the supply of approved registered medicines by trained pharmacists who have undergone specialist accreditation regarding the appropriate use of this product.

6. NZSMI supports the reclassification of proven, safe, effectivce medications from Prescription medicine to Prescription only except when in areas of self-care where quality, global toxicity studies are available, where potential harm can be mitigated, educated about and monitored and where the potential for abuse and misuse is manageable by professional interaction and reporting.

7. NZSMI is aware of and supports the submission from Aspen Pharmacare Limited with specific reference to their melatonin 2mg slow release formulation, Circadin. We see no merit in repeating many of the points made in that submission, but do highlight the following key points, which we believe deserve major consideration:

   (a) The increased availability of Circadin via pharmacist prescription could potentially reduce the number of patients needing to be prescribed benzodiazepines or Zopiclone.

(b) The training that registered pharmacists will receive prior to being allowed to prescribe Circadin will improve the quality of primary healthcare, particularly as it relates to the supply of products for insomnia.

(c) The prescription only except when status is appropriate for products of this level of toxicity and specificity and maintains a good balance between access to useful tools for primary healthcare and self-medication alongside safety and monitoring of potential interactions and side effects.

(d) The pharmacist led process provides a good opportunity for GP referral if this is considered necessary or appropriate.

(e) The period of supply being limited to a maximum of 13 weeks is also appropriate and allows monitoring.

8. Given the relatively small market size that exists in New Zealand for this product, NZSMI supports the over the counter supply via pharmacist prescription of the current Circadin prescription pack, provided patients have been taken through the approved screening tool by a certified pharmacist. This is a balanced, sensible approach to allow appropriate supply of a proven quality product in a suitably controlled environment.

9. Finally, NZSMI does not support melatonin being reclassified to restricted medicine or to be classified as a dietary supplement and believes that appropriate advice and screening is necessary to provide the most appropriate safety umbrella for this medicine.

21 September 2018

The Medicines Classification Committee
Medsafe
PO Box 5013
Wellington 6140

Dear Committee Members,

Re: MCC 61st meeting consultation

Thank you for the opportunity to provide comments on the agenda items for the 61st meeting of the MCC.

5.1.1 Modified release paracetamol

We strongly recommend that paracetamol modified release remains a pharmacy only medicine. Modified release paracetamol provides extended pain relief that is important in osteo-arthritis, for example allowing dosing at bedtime to provide coverage through the night and on waking in the morning, or for a day of activity.

Pharmacists and pharmacy assistants are extremely well-versed in advising on paracetamol, regularly advising on the appropriate and safe dosing and the need to avoid doubling of ingredients. Research showed this to be a clear priority for pharmacy with liquid paracetamol,(Gauld and Sullivan 2018) and anecdotally, with other forms of paracetamol. Under-graduate teaching at pharmacy schools emphasizes the need to counsel with paracetamol. Teaching in the Green Cross Health training academy, Teach Me, also emphasises this for paracetamol products. There are currently more than 6,000 pharmacy staff enrolled on the Green Cross Health Teach me platform who have access to the paracetamol training tools.

The data in the Medsafe report indicates a low level of calls to the Poisons Centre in New Zealand over a 10 year period. We consider the benefit-risk ratio for paracetamol modified release in New Zealand would be at least as favourable as that found with some other pharmacy-only medicines.

We are aware that the main reason that this is being reviewed by Medsafe is due to a decision having been taken relating to a concern in Sweden. We note significant differences to New Zealand in the indication, poisoning reports, and management of overdose. When reviewing data within New Zealand, there is also a significant difference in the pain for which it is indicated in comparison to Sweden, only being osteo-arthritis. We also note, from the GSK objection, that Denmark has taken a different decision to Sweden on the basis of having an appropriate guideline in place, which seems reasonable.

We are also pleased to see that a number of the recommendations made by the MARC review published in December 2017 have already been addressed by the manufacturer.

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We understand that the New Zealand Guidelines used at hospitals in New Zealand for paracetamol overdose have included modified release products for many years, which is important to appropriate management. No deaths are reported in New Zealand by CARM with this product. Training and information sharing by the manufacturer is ongoing with the pharmacy team and the material used is evidence-based with key messages around safe, responsible and appropriate use by patients.

We consider that the proposed up-scheduling of paracetamol modified release would affect access for patients who appear to be using the product appropriately with input from a well-skilled pharmacy team. We have used training information with pharmacy teams including the pharmacist and pharmacy assistants and will continue to emphasize the importance of ensuring patients understand the maximum six tablets per day dosing and not to double up on ingredients. We know pharmacy is very focused on this already, but we recognise the importance of the role of pharmacy in supporting the consumer's safe use of medicines, and being responsive to the concerns of Medsafe and MARC.

Item 5.3 Melatonin

We do not support a "restricted medicine" classification for melatonin. We prefer the alternate proposal in 6.1. The MCC has previously observed that insomnia can be a longer consultation in general practice with underlying conditions needing consideration, and a need to avoid use in children. The 6.1 proposal will help to enable a longer consultation and appropriate consideration of the potential for underlying causes needing referral.

As always, we want pharmacists to have the tools that will maximise the patient benefit of reclassifications. While pharmacists have training at an undergraduate level on sleep hygiene and prescription and non-prescription insomnia treatments, the Aspen proposed model supports a best practice model of care. It uses an evidence-based screening tool, the doctor is informed of supply (unless the patient opts out) or is sent the screening tool (with patient permission) for referrals, with different parts of primary care collaborating to enhance patient care. This model aids the pharmacist to identify red flags in a systematic way, provide thorough advice and a proven treatment (licensed 2 mg prolonged release melatonin). The proposed wording in 6.1, specifying the 2 mg prolonged release tablet will minimise the risk to the patient of an inadvertent supply of a section 29 product.

The restricted medicine category for melatonin holds risk for the public of purchase of unregistered product through the internet. As highlighted by Medsafe, most recently in 2017, such supply has no health professional diagnosis, management or advice and no certainty of quality.(Medsafe 2017) There is risk to anyone of getting melatonin in this way. A particular concern if the restricted medicine category is used is the increased use of melatonin that we would expect to occur in children with no medical input, through purchase of melatonin from overseas via the internet.

Item 6.1 Melatonin prolonged release 2 mg tablets

We strongly support this reclassification to "prescription except when" using the wording proposed in the application. Insomnia is a common and important condition in the population, with ramifications on people's health and quality of life.(Morin, Jarvis et al. 2007) As the existing products (herbals and sedating antihistamines), suffer from a lack of high quality evidence of effect,(Morin, Jarvis et al. 2007) there is a need for a proven treatment to be available through pharmacists. Sedating antihistamines, which are available as pharmacist-only medicines for sleep, are not recommended in the elderly and tolerance to the benefit occurs quickly (but adverse effects can continue).(Morin, Jarvis et al. 2007) Antidepressants are sometimes used for insomnia but have limited evidence.(Morin, Jarvis et al. 2007)

Benzodiazepines and z-drugs are used in high amounts in NZ, despite risks that include falls and motor vehicle accidents,(2015) and possible increased risk of hip fracture.(Khong, de Vries et al. 2012; Bakken, Engleland et al. 2014) In 2013-2014, 120 dispensing per 1000 patients occurred for zopiclone. (2015) We expect that involving pharmacists more in appropriate screening and supply of prolonged release melatonin where necessary could reduce the demand for and prescribing of zopiclone and benzodiazepines. We also see an important opportunity for pharmacists to discuss sleep hygiene and other non-pharmaceutical measures to help patients with a frustrating condition.

We appreciate the consultation that has been undertaken by the applicant on this model of care. We consider this model will strongly support pharmacists to maximise the patient benefit, whether it be identifying that there may be an underlying cause requiring referral, providing the medicine with useful advice, or simply providing sleep hygiene advice, as required. A key point will be in reiterating at the outset the inability to supply any section 29 products, and we will make this very clear to our members in our communications.

6.2 Dextromethorphan, opium tincture, squill oxymel and pholcodine – proposed reclassification from general sale and pharmacy only medicines to restricted medicines

We greatly appreciate the work Medsafe has done in considering these medicines. It is clear that action needs to be taken on Gee's linctus and dextromethorphan, but we believe that pholcodine could remain pharmacy-only as we could not find indications of abuse/misuse, similar to the Medsafe paper.

We support the upscheduling to restricted medicine for opium tincture and squill oxymel. We are aware from pharmacist feedback that many are choosing to keep Gee's linctus off the self-selection shelves and in some cases record the supply. We consider that Gee's linctus provides at least as much danger as dextromethorphan, potentially causing inadvertent drug addiction with 33 mg of morphine in a 200 mL bottle. We recommend that the requirement of an approved pack is removed for this medicine to allow pharmacists to supply small quantities according to their professional judgement, rather than be fixed to the 200 mL currently available. We recommend that the entry wording change (see the track changes version below) in addition to the upscheduling:

"In medicines for oral use containing not more than 0.2% of morphine, when combined with 1 or more active ingredients in such a way that the substance cannot be recovered by readily applicable means, or in a yield that would constitute a risk to health, ~~when sold in a pack approved by the Minister or the Director-General for distribution as a pharmacy-only medicine~~in up to 200 mL."

Dextromethorphan has had misuse internationally, as stated in the Medsafe report, and this had been increasing, although indications suggested it had plateaued in the US.(Anonymous 2012) While discussed particularly in the US where sales are uncontrolled (similar to the general sales category it has in New Zealand), misuse has occurred in other countries also. For example, the upscheduling of dextromethorphan to prescription medicine in Denmark occurred in response to a death following misuse.(Gauld 2013) In Canada, Antoniou and Juurlink(Antoniou and Juurlink 2013) reported 9.7% of students grades 7 to 12 reported using dextromethorphan recreationally in 2013, nearly a 50% increase on the 2011 survey results. These authors also reported that withdrawal can occur for people who have been using it long-term. In Canada, dextromethorphan is available in a general sales setting.

Dextromethorphan is metabolized by CYP2D6, indeed, it is used in clinical trials to ascertain interaction potential for CYP2D6. Those people lacking CYP2D6 can have problems metabolising it and therefore have toxicity from taking five to 10 times the recommended doses,(Anonymous 2012) as could happen in misuse situations. Stockley's Drug Interactions reports an 18 to 27-fold increase in bioavailability in

healthy volunteers given fluoxetine 60 mg/day for eight days and a single 20 mg dose of dextromethorphan; even 20 mg reduced the metabolism considerably. Paroxetine also impairs the metabolism of dextromethorphan, with the ratio of dextromethorphan to its main metabolite in the urine increasing 8-fold. Additionally, there is a risk of serious serotonin syndrome, so these combinations are not recommended. In cases of overdose, e.g. deliberate misuse of higher dosages than recommended, such an interaction would be unhelpful, as with the toxicity mentioned above in people lacking CYP2D6. This adds a further reason to have greater control over supply.

We have interviewed pharmacists from 13 Green Cross Health pharmacies in different communities throughout New Zealand to better understand the experience within the pharmacy. Please see the confidential attachment. We note that the experiences vary across the pharmacies, with no known problem with pholcodine, and some concerns with Gee's linctus and dextromethorphan in some of the pharmacies. These varied in apparent frequency. Pharmacist-only medicine status was seen by most pharmacists as being helpful for Gee's linctus, often reflecting the action already taken by the pharmacist. Additional control was supported by pharmacists with dextromethorphan. It was also thought that providing information to pharmacists and pharmacy staff on the misuse of dextromethorphan was helpful, being unknown to some pharmacists who we talked to. We will be sending advice to our member pharmacies on this and suggesting that the pharmacy organisations do the same.

Pholcodine abuse in NZ pharmacy seems to be unknown, and as Medsafe reports, it has low addiction potential being not metabolised to morphine. The pharmacists we spoke to could not see any need for upscheduling, but an increased burden for the patient to wait for the pharmacist to be available, and for the pharmacist to be involved in every supply. We therefore recommend that this remains a pharmacy-only medicine.

We recommend that dextromethorphan is up-scheduled to a pharmacy-only medicine with a minimum age of 18 years of age for the supply. There is a NZ precedent for this occurring, which is the availability of sildenafil with an age limit of 35-70 years. The intention of the lower age limit was to minimise use in men without ED. Similarly, having a minimum age of 18 years for dextromethorphan would reduce the risk of purchase by those most likely to misuse it. Most teenagers under 18 years with a genuine need will not self-purchase but still have a parent or caregiver purchasing medicines they might need. For the rare instances of a teenager under 18 years of age with a legitimate need to purchase, there will be other ingredient options they can purchase. We note that the minimum age of 18 years appears to have been useful in the US, as discussed in the Medsafe report. The minimum age started in California in 2012 and has been implemented in many other states since then.

Should the minimum age and pharmacy-only medicine classification be implemented for dextromethorphan, it will be easy for pharmacy staff to ask for proof of age if necessary. This will minimise the burden on the consumer and pharmacist for the great majority of people who are using it appropriately. We recommend pharmacy organisations provide good advice to pharmacists about the potential for abuse, and a minimum age of 18 years (if that is used as we propose). We would be sending out multiple messages to pharmacy and through our training academy to support this. One possibility is to try it and reconsider how effective it has been in one or two years. We would be happy to report back from our members about whether they have found this effective in resolving the problem, similar to that provided as an attachment, or through a survey of more members.

In summary, for the 61st meeting, we recommend maintaining the pharmacy-only status for modified release paracetamol. We recommend following the Aspen proposal for melatonin prolonged release, prescription except when…. We also recommend retaining the current pharmacy-only classification for

pholcodine and upscheduling dextromethorphan to pharmacy-only with a minimum age of 18 years, and Gee's linctus to pharmacist-only.

Thank you for considering these views.

Yours sincerely,

[redacted]

Lauren Kilkolly

Professional Services Manager

Green Cross Health

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Johnson & Johnson Pacific

21st September 2018

Medicines Classification Committee
Medsafe
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Dear Sir/Madam,

Re: Item 6.2 Dextromethorphan, opium tincture, squill oxymel and pholcodine – proposed reclassification from general sale and pharmacy only medicines to restricted medicines

Johnson & Johnson (New Zealand) Limited appreciates the opportunity to provide comment on agenda item 6.2 review of dextromethorphan, opium tincture, squill oxymel and pholcodine reclassification, to be discussed at the 61st meeting of the medicines classification committee.

Johnson & Johnson (New Zealand) Limited is the sponsor of Benadryl PE Dry Cough and Nasal Decongestant (TT50-8174) and Codral Cold & Flu + Cough Day & Night (TT50-8125). Benadryl contains Dextromethorphan (10mg/5mL) in combination with Phenylephrine Hydrochloride (5mg/5mL) and Codral contains a day tablet with a combination of Dextromethorphan (10mg), Paracetamol (500mg) and Phenylephrine Hydrochloride (5mg) and a night tablet with Dextromethorphan (10mg), Paracetamol (500mg) and Chlorpheniramine maleate (2mg). These products are indicated for the short-term relief of symptoms associated with cough and cold and are harmonized across both New Zealand and Australia as Pharmacy Only medicines.

Johnson & Johnson (New Zealand) Limited also markets single active pholcodine cough products. Benadryl Dry, Tickly Cough oral solution (1mg/mL) (TT50-6811/1) was available in New Zealand but was discontinued in 2015. Benadryl Dry, Tickly Cough Forte (AUST R 203499) (4mg/mL) is available in Australia only. This product is indicated for cough suppression.

Johnson & Johnson (New Zealand) Limited do not market any medicines containing opium tincture or squill oxymel. This submission will only relate to Dextromethorphan and Pholcodine.

Dextromethorphan

Johnson & Johnson (New Zealand) Limited do not support the reclassification of dextromethorphan (DXM) to a restricted medicine. The proposal provides limited evidence to suggest there is an increase of DXM abuse or misuse with cough products in New Zealand through current classifications. Global regulatory authorities and [redacted] also suggest that there has not been an increase of the incidences abuse/misuse to justify the proposal to reclassify to a restricted medicine. Reclassification is an assessment of benefit vs risk. Given there are only 3 reports of abuse from CARM, and minimal cases reported to the National Poisons Centre in the last 7 years,

we don't believe risk has increased and outweigh the benefits. It is important for consumers to have access to effective products to provide relief for self-limiting conditions. At recommended doses, dextromethorphan is recognised as having a good safety and efficacy profile. Restricting dextromethorphan would impact the availability of products that can help relieve consumers suffering from cough symptoms.

Dextromethorphan acts as a cough suppressant. It is a synthetic morphine derivative that has no significant analgesic, respiratory depressant or physical dependency properties at recommended doses.[1,2] It acts centrally on the cough centre in the medulla oblongata to elevate the threshold for coughing thereby alleviating the symptoms.[1,2] The major metabolite of dextromethorphan, dextrorphan, binds with high affinity to σ-receptors to produce the antitussive activity without exhibiting the classic opiate effects that occur from binding into μ- and δ-receptors.[1,2] As stated in Medsafe's proposal, dextromethorphan toxicity occurs in a dose dependent fashion, but at high doses, can exert mixed clinical psychoactive effects, eliciting both euphoria and dysphoria, distorted visual perception, loss of motor co-ordination, dissociative sedation and vomiting.

In the early 2000s concerns emerged about recreational abuse of dextromethorphan, particularly in adolescents and in combination with alcohol, which brought this issue to the attention of some health authorities and the World Health Organization (WHO). This is further outlined below.

Use of Dextromethorphan- Global Regulatory Authorities Position

WHO Review

Authorities at the World Health Organization (WHO) reviewed the issue about the intentional abuse of dextromethorphan, particularly in young people and in combination with alcohol in 2012.

The pre-review report from the 35th meeting of the Expert Committee on Drug Dependence (ECDD) stated that "*Dextromethorphan is used recreationally. Dextromethorphan produces a range of toxicities depending upon either the dose or the components of the specific formulation that was ingested. Cases of recreational abuse of dextromethorphan have been reported in United States, Sweden, Australia, Germany, and Korea primarily among adolescents and young adults. However, these reports are still relatively infrequent."*

WHO ECDD concluded in 2012 that '*the abuse potential of dextromethorphan is relatively low, intoxications are rare, and reports of dependence are infrequent. Dextromethorphan is widely used as an antitussive agent and placing it under international control could negatively impact its availability for medical use. On this basis, the Expert Committee concluded that a critical review is not warranted at this time.'* No changes were taken on an international scale and Dextromethorphan was not included in the international list of controlled drugs. [3]

USA

In the USA, 14 States have passed laws restricting the sale of DXM to anyone under 18 years of age. Similar federal legislation has also been proposed. Other actions taken by industry to reduce potential DXM abuse include parent education and engagement, as well as efforts across various channels to increase teen perceptions of risk/social disapproval of DXM abuse. These efforts have largely been successful, as data in the USA demonstrates the rates of teen abuse declining or remaining low over the last few years. [4] It is important to note that DXM abuse appeared prominently in the USA and further restrictions were not placed on the sale of DXM, but rather educational programs were put in place.

Canada

A review of dextromethorphan was considered following the recommendations in a 2011 Coroner's report on two deaths from accidental overdose with DMX cough containing medicines. Following the review, there was no change to the classification of DMX cough medicines. In Canada, dextromethorphan is classified as an OTC pharmacy medicine (equivalent to NZ Pharmacy Medicine) in all states except Quebec.

Europe

As indicated in Medsafe's proposal, Europe reviewed dextromethorphan abuse in 2016. Overall, it was determined that the benefit-risk balance of the medicinal products containing dextromethorphan is unchanged subject to a proposed warning to product information.[5] The review did not warrant more marketing restrictions on products containing Dextromethorphan.

Most European countries have retained the non-prescriptions status of dextromethorphan, although there are a small number of exceptions. Dextromethorphan is not registered or marketed in Sweden and was reclassified to a prescription medicine in Denmark in 2008 and France in 2017 due to local reports of misuse/abuse.[6]

Summary

The global data available shows that the abuse potential of dextromethorphan is low. Countries like the USA, Canada and Europe have safely maintained the supply of DXM. Medicines containing Dextromethorphan are common in cough medicines globally and are recognised as having a good safety and efficacy profile.

Abuse Concerns of Dextromethorphan- New Zealand and Australia

New Zealand

The Medsafe proposal makes references to concerns about abuse and reports of misuse of dextromethorphan. However, there is no transparency to the details or evidence of the concerns highlighted within the proposal. If reclassification is proposed, there needs to be robust evidence demonstrating new or an increased rate of abuse to warrant rescheduling of Dextromethorphan. The evidence presented from the National Poisons Centre and the Adverse Reactions Monitoring database do not indicate new significant evidence to suggest there is an increase of abuse or misuse.

The Medsafe proposal does not identify strong evidence of misuse or abuse of dextromethorphan in New Zealand. The primary evidence showed:

1. National Poisons Centre (NPC): 18 calls between August 2011 and June 2018 (7 year period) that were classified as "abuse" or "intentional". Of the 18 calls, 15 were in relation to Dextromethorphan. This averages out to about 2 cases per year over 7 years.
2. Adverse Reactions Monitoring (CARM) database: 3 reported incidents involving cough medication, with the most recent report in 2011. It could be argued this data contains isolated events. There are unknown factors which include the doses taken or if the cases involved misuse of other drugs.

The evidence from the NPC and CARM do not suggest there is abuse or misuse of dextromethorphan. The MCC should not consider reclassification based on these reports.

Johnson & Johnson (New Zealand) Limited

Within the New Zealand market, Johnson & Johnson (New Zealand) Limited markets Benadryl PE Dry Cough and Nasal Decongestant (TT50-8174) and Codral Cold & Flu + Cough Day & Night (TT50-8125). Benadryl contains Dextromethorphan (10mg/5mL) in combination with Phenylephrine Hydrochloride (5mg/5mL). Codral contains a day tablet with a combination of Dextromethorphan (10mg), Paracetamol (500mg) and Phenylephrine Hydrochloride (5mg) and a night tablet with Dextromethorphan (10mg), Paracetamol (500mg) and Chlorpheniramine maleate (2mg). Both products are marketed as Pharmacy Only medicines and have been available since 2009.

[redacted]

[redacted]

Australia

In Australia, Dextromethorphan is a Schedule 2 (Pharmacy Medicine) and is included in OTC medicine monograph. Medicines that comply with the monograph can be registered through a new medicine pathway with a reduced evaluation by the TGA. The safety and efficacy of dextromethorphan has already been assessed and approved by the Over-The-Counter section at the TGA and deemed appropriate at the current levels.

[redacted]

[redacted]

[redacted]

Summary

Dextromethorphan is a well-established, safe and effective cough suppressant that has a long history of safe and appropriate use in New Zealand, Australia and globally. There is no robust justification that would warrant reclassification of Dextromethorphan in New Zealand. Any decision made by MCC needs to be based on new or increased compelling evidence. The use of these medicines is substantially safe for short term treatment of cough and the potential for harm from inappropriate use is low.

The concerns that Johnson & Johnson (New Zealand) Limited has with the scheduling proposal included:

1. There is no robust evidence used to support abuse or misuse of Dextromethorphan to justify reclassification in New Zealand. Reclassification should clearly identify the characteristics of misuse and abuse and the resulting health consequences.
2. [redacted] global regulatory authorities do not show an increase of abuse or misuse of Dextromethorphan.

Johnson & Johnson (New Zealand) Limited disagree that dextromethorphan should be reclassified as a restricted medicine based on the following:

- [redacted] Johnson & Johnson (New Zealand) Limited remains confident that when used according to the approved product labelling, the evidence indicates dextromethorphan-containing products to be well-tolerated and effective and current classification should remain unchanged.
- Given abuse potential is relatively low and that subjecting dextromethorphan-containing products to additional controls to restrict supply would impact availability of a safe and effective ingredient that can help relieve consumers suffering from cough and cold symptoms.
- Cough and cold products containing dextromethorphan continue to demonstrate a positive benefit-risk profile.

Pholcodine

Johnson & Johnson (New Zealand) Limited do not support the rescheduling of Pholcodine to a restricted medicine. There is insufficient detail provided in the proposal to allow key stakeholders to address specific issues of abuse that warrant reclassification. The proposal also highlighted concerns between pholcodine use and anaphylactic reactions to neuromuscular blocking agents during surgery. Again, the proposal provided insufficient detail to warrant reclassification.

Pholcodine is an alkyl ether of morphine that was formed by the replacement of the phenolic hydrogen atom with morpholinoethyl group and is related to codeine.[7,8] It is a centrally acting cough suppressant.[9,10] Hence, unlike morphine and other opioids, the depressant effects of pholcodine on the respiration are less and has little or no analgesic or euphorigenic activity. As stated in Medsafe's proposal *"there seems to be a consensus that the addictive potential of pholcodine is low".* Pholcodine is a useful cough suppressant without the safety concerns associated with strong opiates such as codeine and morphine.

<u>New Zealand and Australian Markets</u>

Pholcodine is a well-established, safe and effective cough suppressant that has a long history of use and has been available in New Zealand and Australia for many years. It is available as a Pharmacy Only medicine in New Zealand and as a Schedule 2 (Pharmacy Only) in Australia.

The Medsafe proposal does not identify strong evidence of misuse or abuse of Pholcodine in New Zealand. The primary evidence showed:

1. National Poisons Centre (NPC): 18 calls between August 2011 and June 2018 (7 year period) that were classified as "abuse" or "intentional". Of the 18 calls, 2 were in relation to Pholcodine. It could be argued these are isolated incidents.
2. Adverse Reactions Monitoring (CARM) database: 0 reports involving Pholcodine

The evidence from the NPC and CARM do not suggest there is abuse or misuse of Pholcodine. The MCC should not consider reclassification based on these reports.

Johnson & Johnson have two formulations that contain the single active of Pholcodine. Benadryl Dry, Tickly Cough oral solution (1mg/mL) (TT50-6811/1) was registered in New Zealand in 2010 but was discontinued in 2015. In Australia, Johnson & Johnson Pacific (JJP) market Benadryl Dry Tickly Cough Forte, containing Pholcodine (4mg/mL) and has been available as a Pharmacy Only medicine since 2013. [redacted]

[redacted]

The Medsafe proposal does not include specific evidence to suggest abuse/misuse of Pholcodine within New Zealand. [redacted]

Pholcodine and Anaphylactic Reactions to Neuromuscular Blocking Agents

The Medsafe proposal referred to the link between severe allergic reactions to neuromuscular blocking agents during surgery and previous pholcodine exposure. The proposal also referred to the most recent action taken by the French regulatory agency to reschedule any Pholcodine containing medicines to prescription. As above, the proposal does not present robust evidence to support this is an issue in the New Zealand market.

The European Medicines Agency published an assessment report that reviewed the safety of pholcodine and the pholcodine NMBA anaphylaxis hypothesis. The review concluded[11]:

"the evidence in support of an association between pholcodine and NMBS related anaphylaxis is circumstantial, not entirely consistent and does not support the conclusion that there is a significant risk of cross-sensitisation to NMBAs and subsequent development of anaphylaxis during surgery. Further data needs to be generated to clarify the possibility of an association between pholcodine use and NMBA-related anaphylaxis."

In Australia, the above issue was also discussed and the TGA shared EMAs view that further data is needed to establish the link between pholcodine and NMBA related anaphylaxis.

The present evidence shows that the link between Pholcodine and NMBA related anaphylaxis is extremely low. Pholcodine is a well-recognized cough suppressant with minimal safety concerns. The MCC should not reclassify Pholcodine based on limited evidence.

Recommendation

Overall Johnson & Johnson (New Zealand) Limited believe that the evidence demonstrates that there is no increase of abuse/misuse of either Dextromethorphan or Pholcodine to justify reclassification to a restricted medicine. Countries like the USA, Canada and Europe have safely maintained the supply of Dextromethorphan. Both Pholcodine and Dextromethorphan are still considered an effective cough suppressant with minimal safety concerns. The current scheduling remains justified as the benefits outweigh the risks.

If despite the above, MCC decides that the benefits of DXM and Pholcodine do not outweigh the risks for cough and cold products we request that MCC grant a 2-year implementation timeframe to consider the seasonal nature of Dextromethorphan and Pholcodine containing cough and cold products and supply complexities.

Johnson & Johnson (New Zealand) Limited would like to thank the MCC for this opportunity to provide comment on the scheduling proposals for Dextromethorphan and Pholcodine in New Zealand. Please feel free to contact me should you need further information.

Yours faithfully,

[redacted]

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21 September 2018

Chair, Medicines Classification Committee

Dear Chair,

Re: Reclassification of modified-release paracetamol to restricted medicine

The Clinical Risk Branch of Medsafe supports the recommendation of the Medicines Classification Committee (MCC) on 26 April 2018 to reclassify modified-release paracetamol from pharmacy-only to pharmacist-only (restricted) medicine.

The Clinical Risk Branch of Medsafe does not consider that the objections raised by GSK are sufficient grounds for the Committee to reverse this recommendation. GSK has not provided new safety information and therefore the benefit-risk balance is unchanged.

GSK's objection is based on two key points:

- The marketing authorisation for modified-release paracetamol has been reinstated in Denmark.
- The guidelines for treating modified-release paracetamol overdose in New Zealand are different from the Swedish guidelines that were shown to be inadequate in the Salmonsen Study [1].

We note that the GSK objection suggests that the company agrees that modified release paracetamol is more problematic in overdose.

The Danish Medicines Agency decided not to suspend the marketing authorisation of modified release paracetamol in Denmark in May 2018. The Agency considered that the treatment guidelines for modified-release paracetamol overdose in Denmark are sufficient to prevent liver injury. The Danish guidelines recommend that all patients suspected of paracetamol overdose are started on acetylcysteine. Serum paracetamol concentrations are then used to determine the duration of treatment. Modified-release paracetamol is classified as a **prescription** medicine in Denmark. The European position was to suspend the marketing authorisation for these products. The proposal submitted to the MCC was merely to change the classification to restricted medicine.

The current *Guidelines for the management of paracetamol poisoning in Australia and New Zealand* [2] do not adequately take into account the unpredictable and prolonged absorption of the modified-release formulation. Serum paracetamol concentration may peak as late as 24 hours after ingestion of modified-release paracetamol.

Similar to the Danish guidelines, the Australian and New Zealand guidelines currently recommend administration of acetylcysteine in all patients who have ingested more than 200 mg/kg or 10g (whichever is lower) of modified-release paracetamol. The serum paracetamol concentration should be measured at least 4 hour after ingestion, and again 4 hours later. If either concentration is above the nomogram line, acetylcysteine should be continued. If both concentrations are below the nomogram line and are decreasing the acetylcysteine may be discontinued; otherwise, the acetylcysteine should be continued for the full 21 hours.

The Medicines Adverse Reactions Committee (MARC) discussed the risk of overdose with modified-release paracetamol at the 172nd meeting on 7 December 2017 (minutes available at www.medsafe.govt.nz/profs/adverse/Minutes172.htm#3.2.2).

The MARC noted that after a large overdose of modified release paracetamol peak blood concentrations may not occur until 24 hours, which may be after completion of the traditional acetylcysteine course. Thus the patient's liver will not be fully protected by the antidote if the current guidelines are followed.

The MARC recommended that the New Zealand guidelines for paracetamol overdose should be updated. The guidelines group agreed that the current guideline does not provide sufficient guidance on how to manage overdose with modified-release paracetamol and are currently working to update the paracetamol overdose guideline.

It is our view that managing overdose of modified release paracetamol is complex and there is currently insufficient information on how best to manage these patients to prevent liver injury. We therefore consider that modified-release paracetamol should be reclassified as a restricted medicine. This higher level of classification does not limit access to those who require a longer acting paracetamol formulation for analgesia, but it reduces the likelihood that the product will be purchased for the purpose of overdose. The requirement for consultation with a pharmacist will ensure that patients are aware that the dosing schedule for modified-release paracetamol is different to 'normal' paracetamol, and that the product should not be taken in combination with other paracetamol-containing products.

Yours sincerely

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References:

1. Salmonson, H., G. Sjoberg, and J. Brogren, The standard treatment protocol for paracetamol poisoning may be inadequate following overdose with modified-release formulation: a pharmacokinetic and clinical analysis of 53 cases. Clin Toxicol (Phila), 2017: p. 1-6.
2. Chiew, A.L., et al., *Consesus statement: Guidelines for the management of paracetamol poisoning in Australia and New Zealand - explanation and elaboration.* Med J Aust, 2015. **203**.

Submission on behalf of NZ Branch of the Australasian Sleep Association to 61st Medicines Classification Committee, Medsafe NZ on items 5.3 and 6.1

With limited notice we have not been able to consult across the membership of the Association but on behalf of the NZ committee we would offer the following comments:

Melatonin 3mg tablets (Item 5.3):

A variety of strengths and preparations of melatonin are being used widely in NZ from accounts by members and the patients have usually purchased the preparation abroad or imported it by post. At the above strength there have been no concerning signals over safety despite widespread use overseas accepting there have been minimal attempts at post-marketing surveillance as in many countries it is not licensed as a medicine.

It would therefore be a logical and safer approach to make a standard strength, and we would support 3mg tablets, and preparation available in NZ. The efficacy of melatonin for insomnia (it is no longer classified as primary or secondary) is limited.

We would support restriction of sale to pharmacies with pharmacist's offering clear advice to seek medical advice from their GP if a short course of melatonin is unsuccessful or if the patient is requiring to take melatonin long term.

Cognitive behavioural therapies are at least as effective and probably more effective than pharmacological therapies in most patients with insomnia and it is essential to ensure patients explore alternative approaches at a relatively early stage.

Slow release Melatonin 2mg tablets (Item 6.1):

This preparation has now been available for several years both overseas and in NZ. Its use in NZ has been limited as it is expensive and not funded by Pharmac so most NZ sleep therapists have limited experience of its use. However, overseas evidence is, again, that there are not significant concerns regarding safety with this strength and this slow release preparation.

The evidence base is in older adults and, at best, approximately 25-33% of older patients with sleep re-initiation insomnia have a significant response to this therapy.

Access to this medication should have some restrictions for a number of reasons:

1) There is no convincing evidence of efficacy in sleep initiation insomnia so a health professional should be required to assess the individual's pattern of insomnia and give appropriate advice. The professional could be a pharmacist who had appropriate training in this area.
2) Abrupt onset of sleep re-initiation insomnia can be related to the development of depression. Prior to initiation of this therapy a health professional who should be aware of this possibility needs to discuss with the patient this possibility and consider asking them to fill in suitable questionnaires such as HAD score, PHG-9 and GAD-7. The patient would be strongly advised to show their scores to their GP if abnormal for further advice.

3) The evidence base is in older adults (over 55yrs) and efficacy is limited and a health professional has to discuss these facts with the patient. The health professional should ensure the individual meets the criteria and is aware of limited efficacy and the need to pursue alternative therapeutic approaches and potentially investigation if no clear response to the therapy.
4) We would support a limit on supply (13 weeks is appropriate) and, if continued use of the medication required, then patient must be advised to seek further advice from their GP. We are less certain how reliably such a "caveat" can be enforced but would support its recommendation.

Finally in regard to whether this medication is a food, drug, hormone or neuro-transmitter seems irrelevant in determining the classification. It is a psycho-active substance and thus it is essential its safety is assessed and both dosage and preparations are regulated to avoid the risk of harm to the public.