Consumer Healthcare Products Australia

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1 September 2020

The Secretary
Medicines Classification Committee
Medsafe
PO Box 5013
Wellington 6145
New Zealand

By email to: committees@moh.govt.nz

Dear Sir/Madam,

Intention to object to a recommendation made at the 64th Meeting of the Medicines Classification Committee – Item 6.3 Pholcodine

Consumer Healthcare Products Australia wishes to object to the recommendation made at the 64th meeting of the MCC, to reclassify pholcodine from Pharmacy Medicine to Pharmacist Only Medicine.

CHP Australia has reviewed the minutes of the 64th meeting and is very concerned with the quality of decision making and lack of transparency reflected in the minutes. The minutes, as published on the Medsafe website, should present a true and accurate record of the meeting proceedings. If this is the case, then we hold concerns that the MCC may not have properly considered all of the issues raised; may not have carefully considered all the submissions made by stakeholders during the consultation process, and may have based the recommendation for reclassification on vague and arbitrary grounds rather than a robust review of the evidence in its entirety.

This objection is therefore being made on the grounds that:

- the MCC did not properly consider safety and has placed disproportionate emphasis on theoretical risks
- there was a breach of the appropriate process.

Safety

Decisions to reclassify a medicine should only be made when there is objective evidence of new safety concerns that shift the balance of risk vs. benefit.

In the case of pholcodine, there is no such new evidence, however a decision to reclassify was made irrespective of this, or for other, unrelated reasons.

The MCC considered the classification of pholcodine at the 61st meeting of MCC,[1] held in November 2018. The minutes of that meeting refer to the fact that pholcodine has limited potential for abuse, as well as to the hypothetical nature of the association of pholcodine and anaphylaxis to neuromuscular blocking agents (NMBAs). In the minutes of the 61st meeting of the MCC, the following statements were made:

"*…..A rare but fatal association with anaphylaxis and neuromuscular blockers and pholcodine was discussed but the evidence for this was considered limited*."

"*….the Committee concluded that there were minimal safety concerns around pholcodine and that the current classification is appropriate."*

At the November 2018 meeting, the MCC recommended that the classification of pholcodine should remain unchanged.

Since that meeting, the only additional data considered by Medsafe is the review conducted by the Medicines Adverse Reactions Committee (MARC)[2] in December 2019, which focussed primarily on the "pholcodine hypothesis" which holds that prior use of pholcodine may be responsible for an increased risk of anaphylaxis to NMBAs. The data reviewed by MARC are essentially the same data considered by Medsafe in 2018.

It is clear from the evidence considered as part of this review that this association is hypothetical and circumstantial, and inconsistencies and uncertainties remain. Other agents such as personal care products, cosmetics and other environmental agents that contain quaternary ammonium ions (QAIs) as part of their molecular structure may also play a role in sensitisation and the evidence of a causal relationship with pholcodine is not strong.

The Australian and New Zealand College of Anaesthetists' submission was the only one out of 8 submissions that supported the reclassification of pholcodine. However, no new published or peer reviewed data indicating that there is a causative link between pholcodine and anaphylaxis to NMBAs were provided. The submission quoted reports from the CARM database of 62 cases of NMBA anaphylaxis between January 2017 and June 2019 together with reports of elevated pholcodine-specific IgE in 54% of cases, however these case reports have no context, do not prove causation, and do not address the inconsistencies in the hypothesis as a whole.

The pholcodine hypothesis has been the subject of much discussion since the first papers were published more than a decade ago, and the evidence base has not shifted significantly since that time.

The most recent published survey data from the Australian and New Zealand College of Anaesthetists (ANZCA)[3] states that anaesthesia morbidity and mortality is extremely

[1] https://www.medsafe.govt.nz/profs/class/Minutes/2016-2020/mccMin2Nov2018.htm
[2] https://www.medsafe.govt.nz/committees/marc/reports/180-3.2.1-Pholcodine.pdf
[3] ANZCA Australian and New Zealand College of Anaesthetists (2017). Safety of anaesthesia. A review of anaesthesia-related mortality reporting in Australia and New Zealand 2012-2014.

low and anaesthesia has never been safer. It states that the most important factor contributing to mortality during anaesthesia was the severity of the patient's underlying medical condition.

The MCC minutes of the 64th meeting align with these conclusions and state:

".....It was noted that anaphylaxis is rare and neuromuscular blocking agent anaphylaxis is rarer again. A person would have to have repeated exposure to be at risk and that exposure can come from a number of substances in the environment. The causality is unclear."

Overall, the minutes of the meeting do not refer to any new safety concerns. Pholcodine is not the subject of abuse, drug dependence or misuse. The adverse event profile is well known and there are no new safety issues reported.

It therefore seems inconsistent that the MCC has recommended reclassification of pholcodine in the absence of any new supporting evidence of emerging safety concerns relating to NMBA anaphylaxis. The minutes state:

"....The change in classification may not mitigate the risk of anaphylaxis under anaesthetic, as the sensitisation may occur from exposure to a number of substances, but the interaction with the pharmacist may reduce the risk to the individual person."

Additionally, the MCC noted that:

"....the connection with neuromuscular blocking agents is not clear due to other environmental factors".

It can be concluded from these statements that the decision to reclassify pholcodine was therefore not made to mitigate any demonstrated safety issues. Instead, the MCC justifies its decision in the following way:

".... It was noted that most submitters opposed the reclassification but the chance to reduce the volume used by intervention of a pharmacist may be useful."

CHP Australia asserts that this is not an example of evidence-based decision making. It suggests that people are accessing pholcodine when they don't need to, when there is no evidence of misuse or inappropriate use. Additionally, it appears that the MCC is of the view that the volumes currently supplied are too high, and there is no evidence for this being the case.

There was not widespread support for reclassification. It was opposed by the New Zealand Pharmaceutical Society. The decision imposes logistical and workflow demands on pharmacists, who will now be required to record in their dispensing software every occasion of supply of a cough suppressant in New Zealand. It will unnecessarily inconvenience and disadvantage consumers.

It should also be noted that the current classification of pholcodine as a Pharmacy Medicine is still supervised; the advice of a pharmacist is still available for consumers who need it and pharmacy staff undergo training. It is a healthcare environment and is not unsupervised sale. We also note that the New Zealand Pharmaceutical Society was of the view that it is unlikely that any health professional providing or prescribing

pholcodine will know whether it will trigger a theoretical increase in IgE for that particular patient, and that any risk mitigation is more appropriately done at the pre-anaesthetic assessment prior to surgery. This view aligns with the majority of the other respondents.

CHP Australia is very concerned that the decision to reclassify is not evidence based, is disproportionate to risk, and has been made with the clear objective of decreasing sales volumes, in the absence of any evidence of misuse or inappropriate use.

This in our view does not represent good regulatory decision making and is a clear demonstration that the MCC has not properly considered the well documented and established safety profile of the substance in arriving at this recommendation.

Breach of process

CHP Australia believes that the MCC has not followed appropriate decision-making processes, and this represents a breach of process.

In line with widely accepted principles (e.g. the Australian Administrative Law Policy Guide published by the Australian Government Attorney General's Department[4]), decision making by regulators should generally be fair, high-quality, efficient and effective. Decisions should be explained in a manner which affords people affected by decisions procedural fairness (or natural justice) and decision makers should explain those decisions in a manner which people can understand. Broadly, procedural fairness requires that the decision maker be, and appear to be, free from bias and/or that the person receives a fair hearing.

These principles are also common to the New Zealand Government's document, Government Expectations for Good Regulatory Practice,[5] where many expectations are set out, including that the regulatory system must have clear objectives, seeks to achieve these objectives in a least cost way, and is proportionate and fair and equitable in the way it treats regulated parties.

Good decision making requires an absence of bias, whether actual or perceived, consideration of all relevant matters and disregard of non-relevant matters. CHP Australia believe that the MCC has not followed appropriate administrative decision-making principles in arriving at their recommendation.

Lack of objective decision-making criteria

As a general over-arching concern, CHP Australia is of the view that Medsafe should publish a clear set of criteria that apply to the different classifications. The information published by Medsafe describes what a Pharmacy Medicine is and what a Pharmacist Only Medicine is, i.e. that Pharmacist Only Medicines require behind-the-counter storage, direct pharmacist supervision and recording of sales.

[4] https://www.ag.gov.au/sites/default/files/2020-03/Australian-administrative-law-policy-guide.pdf

[5] https://treasury.govt.nz/sites/default/files/2015-09/good-reg-practice.pdf

However, there are no clear and objective criteria to differentiate how these two classifications should be assigned to different medicines.

Looking at other medicines as examples, generally, the Pharmacist Only Medicine is applied where there are concerns about consumers not being able to correctly diagnose a condition, or where there may be a risk of misuse or abuse, specific contraindications or interactions – hence the requirement to record sales. These factors do not apply to pholcodine and the MCC minutes do not make any assessment relative to any clear differentiating criteria between the two classifications.

Decision is not proportionate to risk

According to the Medsafe guidance document on changing the legal classification of a medicine in New Zealand[6], the MCC considers various principles in determining whether or not to change the classification of a medicine – as described under Phase 1. These principles in effect require the setting out of risk vs. benefit. In relation to the pholcodine decision there are clear issues in how the MCC has assessed risk vs benefit.

The concerns about "masking a cough" are mis-conceived because people who continue to have an unexplained cough will see their doctor rather than take a cough suppressant on a continuing basis. The products are clearly labelled as being for short term use. This is not a new issue that has only now become evident.

In its own statements, the MCC has also acknowledged that the risks of pholcodine in relation to anaphylaxis to NMBAs are uncertain and causality is unclear. The relationship is still hypothetical.

Consumer benefits of access to medicines for minor ailments have not been considered. Efficacy data may be old, but as the MCC states, this does not mean that there is no need for the medicine as there is still consumer demand.

CHP Australia is therefore concerned that in the absence of any new robust data regarding a shift towards increased risk of pholcodine, any decision to reclassify to a higher classification is disproportionate and without proper foundation. There are no clear objectives articulated in justifying the decision, other than it will offer the chance to reduce the volumes used – when there is no evidence of inappropriate use or that the volumes used are high.

Decision was made on irrelevant criteria

As described above, the MCC has stated that the reclassification decision was made to offer the chance of reducing volumes supplied. CHP believes that this is irrelevant, particularly in the absence of any evidence that the products are supplied inappropriately or over-used. In any event, the classification of medicines is intended to provide appropriate oversight based on the risks of a substance or the conditions for which it is used - the classification of a medicine is not a tool for managing sales volumes.

[6] https://www.medsafe.govt.nz/downloads/How_to_change_medicine_classification.pdf

Fair and equitable decision-making

CHP is concerned that 7 out of 8 submissions provided by respondents appear to have been disregarded.

The concerns of the parties most affected by this decision, i.e. industry and pharmacists, do not appear to have been given due consideration. The minutes do not include any assessment or discussion of the objections, nor do they include any rationale to explain why MCC disregarded the objections and why the MCC chose to support the minority view. For pharmacists, recording every sale of a cough suppressant is probably not necessary and these records are not likely to be used or accessed for any specific safety related purpose. The current Pharmacy Medicine access has not been a problem over the past decades and it is unclear what additional public health benefits the proposed reclassification will deliver.

Explanation of the decision

The decision to reclassify is inconsistent with the previous decision and statements made by the MCC in 2018, given that there has been no shift in risk over this time.

The explanation of the decision to reclassify and the reason for this inconsistency with previous decisions is not explained by the minutes.

Here we have a situation where a more recent decision is completely different to an earlier decision and yet is based on the same data. When such a reversal takes place, the decision maker has a clear obligation to those affected by the decision to explain (in detail) how that has occurred.

Conclusion

In reviewing the minutes of the MCC meeting it appears to CHP Australia that there are insufficient grounds for this decision. There have been no new data to suggest a shift in the well-established safety profile of pholcodine. The pholcodine hypothesis, upon which this reclassification is largely justified, continues to be uncertain; the causality unproven, and other environmental factors are also involved.

We have concerns that the MCC has also based this decision on other arbitrary and irrelevant criteria, such as a desire to reduce the volumes supplied. This is an inappropriate use of classification. The decision to reclassify is not proportionate to risk and has no widespread support among other stakeholders.

CHP Australia does not support the MCC's recommendation to reclassify pholcodine to Pharmacist Only Medicine. We request the MCC to reconsider this decision and believe that the current Pharmacy Medicine classification continues to be appropriate.

Yours sincerely

[redacted]

[redacted]

PHARMACY GUILD OF NEW ZEALAND

01 September 2020

Medicines Classification Committee Secretary
Medsafe
Wellington

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

Dear Committee Members

RE: Recommendation made at the 64th meeting of the Medicines Classification Committee

Thank you for the opportunity to provide feedback on the recommendations made at the 64th meeting of the Medicines Classification Committee (MCC), held on 9 July 2020.

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.

We would like to object to the recommendation for

- Agenda item: *6.3: Pholcodine – reclassification from a pharmacy medicine to a restricted medicine (Medsafe)*

As outlined in previous submissions to MCC on 21 September 2018 and 20 March 2020, the Guild **does not** support the proposed reclassification of pholcodine from a pharmacy medicine to a restricted medicine.

We have concerns that there is no clear and justified case for MCC to make the recommendation to change the classification of pholcodine from pharmacy to restricted (pharmacist only). Our concerns are based on:

- the minutes from the 61st meeting, MCC recommending the classification of pholcodine should remain unchanged, and
- the minutes from the 64th meeting, MCC were not able to conclude that the case would definitely lead to the desired outcomes, *"The change in **classification may not mitigate the risk** of anaphylaxis under anaesthetic, as the sensitisation may occur from exposure to a number of substances, but the interaction with the **pharmacist may reduce the risk** to the individual person."*

We believe the recommendation to reclassify pholcodine to a restricted medicine will place an unnecessary burden on the pharmacist to replace a process that is already managed appropriately in a pharmacy.

The current measures and controls in place in community pharmacy are sufficient and effectively manage the unnecessary sale and supply of medicines containing pholcodine. All pharmacy staff are trained to identify uncomplicated dry cough and capable of providing appropriate treatment options to patients. They are also trained to refer on to the pharmacist when further assessment is necessary. All activities in a pharmacy fall under the supervision and responsibility of the charge pharmacist.

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P. 04 802 8200 F. 04 384 8085 E. enquiries@pgnz.org.nz www.pgnz.org.nz

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

Yours sincerely,

[redacted]

Johnson & Johnson Pacific

1st September 2020

Medicines Classification Committee
Medsafe
PO Box 5013
Wellington 6145

Dear Sir/Madam,

Item 6.3 Pholcodine - Reclassification from a Pharmacy Only to a Restricted Medicine (Medsafe)

Johnson & Johnson (New Zealand) Limited (JJNZ) appreciates the opportunity to provide comment on the recommendation made at the 64th meeting of the Medicines Classification Committee (MCC) which recommends that Pholcodine be reclassified from a Pharmacy Only to a Restricted (Pharmacist Only) Medicine.

We are disappointed with the MCC's recommendation and with the quality and transparency of the decision making. We respectfully request that this be considered as a valid objection to the recommendation made by the MCC, as we have concerns that the MCC may not have accurately considered all the issues raised by JJNZ. We believe that the MCC may have based the recommendation for reclassification on subjective grounds rather than a robust review of all new evidence to warrant the shift in the benefit-risk profile, especially as no new evidence was provided at this meeting that wasn't considered at previous meetings.

The grounds for the JJNZ objection include:

- The MCC did not properly consider safety holistically and has placed excessive emphasis on the safety risks

- The appropriate process was not followed to demonstrate the robust reasons why there is a shift in the Benefit-risk profile.

Safety:

the MCC did not consider all the safety issues in a holistic way, and the evidence it has considered has not changed since the decision at the 61st meeting held on 2 November 2018, which deemed the current scheduling as appropriate.

Since the 61st meeting the only additional data considered by MCC is the review conducted by the Medicines Adverse Reactions Committee (MARC) in December 2019, which focussed primarily on the "pholcodine hypothesis" which shows that prior use of pholcodine may be responsible for an

increased risk of anaphylaxis to neuromuscular blocking agent (NMBAs). The data reviewed by MARC is essentially the same data considered by Medsafe in 2018.

In the absence of new evidence, we question the grounds the decision was made to warrant the reclassification of pholcodine. A decision to reclassify a medicine should be made based on objective new safety or efficacy concerns that shifts the benefit-risk profile. If in fact there is **new** confirmed evidence that has not been presented at previous meetings shifting the benefit-risk profile it has not been made clear in these minutes.

At the 61st meeting, the committee concluded:

Pholcodine has limited potential for abuse. A rare but fatal association with anaphylaxis and neuromuscular blockers and pholcodine was discussed but the evidence for this was considered limited. The Committee discussed how OTC medicines sometimes are not perceived by patients as medicines and therefore it is more difficult to identify this when taking a patient's medication history. However, the Committee concluded that there were minimal safety concerns around pholcodine and that the current classification is appropriate.

On the balance, there is no new evidence that puts into question the pholcodine hypothesis. In the countries pholcodine is not marketed the prevalence of IgE to pholcodine was found to be high. This is because the evidence suggest that a broad range of other agents may also be responsible such as household products as included in JJNZ's application and acknowledged by the MCC. Therefore we are unclear how reclassifying pholcodine to Restricted Medicine will mitigate all possible risks, except limit the volume sold which is not aligned with the purpose of the Restricted Medicine classification.

The MCC also raise concerns that pholcodine can "mask a cough". This is mis-conceived because like with any cough medication consumers will see their doctor rather than take a cough suppressant on a continuing basis. The products are clearly labelled as being for short term use. Again, this is not based on new evidence that shifts the benefit-risk profile.

Based on the above, JJNZ believes that the evidence was not considered appropriately by the MCC. In the absence of new evidence and clear minutes on how reclassification would positively impact the outcome, how can the MCC come to a different conclusion than previous without thorough minutes explaining why the previous decision were incorrect? In fact the minutes highlight that the change in classification may not mitigate the risk of anaphylaxis under anaesthetic. Therefore reclassification will not achieve the purpose of the Restricted Medicine classification which is mainly for conditions that are difficult to self-diagnose, or where there may be a risk of misuse or abuse and/or specific contraindications or interactions that requires pharmacist intervention. This is not the case with pholcodine. All that the reclassification will set to achieve is reduction in volume sold.

Efficacy:

It is unjustified to base any decisions on the fact that efficacy data for pholcodine is weak and old. As detailed in the JJNZ submission, Pholcodine has a long history of safe use and we wish to highlight that there are many medicines that are old "grandfathered" medicines that continue to be safely used without reclassification. In addition to there being no new safety evidence, there has been no new efficacy evidence to warrant a shift in the benefit-risk profile.

Process:

The minutes of the MCC decision is not detailed and does not provide the reasons for the decisions in an objective manner. The MCC has not considered new evidence that would shift the benefit-risk profile to warrant a different outcome to previous meetings. In fact, the reasons for the decision do not appear to be aligned with the issues covered in the agenda.

As discussed above, confusingly at the 61st MCC meeting and the Medsafe safety review confirm that pholcodine has limited potential for abuse. However, in these recent minutes the conclusion drawn is contradicted without explanation. If there is new evidence of harm that shifts the benefit-risk profile, then it is fair to expect the evidence detailed in the minutes, however it is absent.

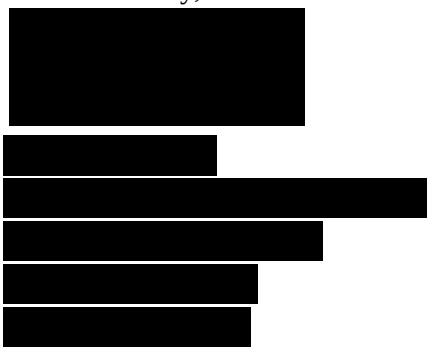
JJNZ also believes that the MCC has not properly considered the impact the reclassification will have on the New Zealand consumer. There will be no dry cough offering over the counter. This could have unintended consequences that the MCC needs to be mindful of. Restricting access to safe and effective pholcodine cough products is likely to eliminate dry cough products from over the counter access. It can drive consumers with dry cough into general practice and increase access to prescription products and this could have negative impact on the public health system and the health budget at a time when over-utilisation of medical services is very difficult to control, and it may potentially drive the inappropriate prescribing and use of antibiotics. It can also drive people to use incorrect products (e.g. salbutamol or a wet cough products), or unregistered cough products simply because consumers cannot find a dry cough product, causing safety concerns.

In conclusion, in the absence of any new evidence regarding pholcodine's efficacy or safety since the MCC decision at the 61st Meeting there is no shift in the benefit-risk profile to warrant reclassification.

We have concerns that the decision is not evidence based and the MCC should provide compelling **new** reasons why reclassification is necessary. The connection to NMBA's still remains unclear due to other environmental factors, and we are not aware of new evidence to suggest abuse, despite it being included in these minutes. JJNZ remains concerned that reclassification is premature and will not address the concerns other than reduce the volumes supplied, which is not a good use of the classification system.

JJNZ respectfully requests the MCC to reconsider this decision until such time there is compelling evidence to suggest otherwise. We maintain that the current Pharmacy Only classification continues to be appropriate.

Yours faithfully,



31 August 2020

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

Sent by email: committees@moh.govt.nz and committees@health.govt.nz

Re: Objection - Recommendation Made at the 64th Meeting of the Medicines Classification Committee

Item 6.3: Proposal for reclassification of pholcodine from a pharmacy medicine to a restricted medicine

iNova Pharmaceuticals (iNova) does not support the proposal to reclassify pholcodine to restricted medicine status.

Please find attached iNova's Objection to the proposed reclassification of pholcodine. This document clearly outlines iNova's rebuttal to the Recommendation made by the Medicines Classification Committee (MCC), using the MCC's criteria for the submission of Objections, and outlining the rationale supporting each specific item raised.

While iNova's Objection provides strong and valid reasoning for retaining the current Pharmacy Only Medicine classification for pholcodine, should this argumentation not be accepted by the Committee, also provided is a request for a 1 year deferral of the gazettal of this change in classification. This deferral is being requested to ease the exceptional pressures being applied in New Zealand pharmacies at this time, because of the ongoing impacts of COVID-19.

Please note, iNova reserve all of our rights and remedies in relation to this matter.

Yours faithfully

[redacted]

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Pholcodine Reclassification Objection

Reasons for Objection

Objection 1

• the MCC did not consider all the safety issues correctly

The Medicines Adverse Reactions Committee (MARC) requested the Medicines Classification Committee (MCC) to consider the "unproven efficacy of pholcodine which is widely used for symptomatic relief of self-limiting, non-serious acute cough due to upper respiratory tract infection, against an unconfirmed but suggestive association between pholcodine and an increased population risk of life-threatening anaphylaxis to [neuromuscular blocking agents] NMBAs in patients undergoing surgery"[i]. In order to appreciate the risk of anaphylaxis to NMBAs, this should be considered in the broader context of the risks associated with surgery. The MCC minutes qualitatively comment that anaphylaxis is rare and neuromuscular blocking agent anaphylaxis is rarer again, but do not provide that important context, which enables risk: benefit to be appropriately determined. Quantification of the risks reveals that they are very small.

1. Anaesthesia-related mortality

In Australia for the period 2012-2014 there were about 11.40 million individual episodes of anaesthesia care for a population of 22.52 million (ANZCA, 2017)[ii]. The **anaesthesia-related mortality rate was 2.96 deaths per million population per annum** and is very similar in all triennium reports since 1997-99 (ANZCA, 2017). The preamble to the 2012-2014 report states: "*Anaesthesia in Australia and New Zealand has never been safer for our patients."* For the 3-year period 200 deaths were reported. Patients assessed as higher risk accounted for 93% (186/200) of anaesthesia-related deaths. Since 2000 there has been a progressive increase in the percentage of deaths, in which the patient's chronic medical condition was deemed to have contributed to the death, rising from 28% of cases in the 2000-2002 triennium to 86% in the 2012-2014 reporting period. Thus, the **most important factor contributing to mortality was the severity of the patient's underlying medical condition**. Most deaths also occurred in older patients, with 52% of patients aged over 80 years and 20% over 90 years. Seventy-three per cent (73%) of the anaesthesia-related deaths (146/200) also occurred in patients having procedures classified as urgent or emergent. **Therefore, urgent or emergent surgery remains a major risk factor for anaesthesia-related deaths**.

These Australian and New Zealand College of Anaesthetists (ANZCA) data illustrate two important points. Firstly, as ANZCA observe "**anaesthesia mortality rates in modern Australia are low and that anaesthesia risk is now extremely low in patients who are fit and well**." There is no reason to believe that a similar conclusion could not be made for New Zealand. Given this assessment, the presence of pholcodine specific IgE, elevated or otherwise, in these patients is unlikely to change this risk profile. Secondly, ANZCA also note that there has been a progressive increase in the percentage of deaths where the patient's chronic medical condition was deemed to have contributed to the death. ANZCA conclude "there may have been some cases in which the decision to operate was inappropriate or futile." Thus, improving the mortality rate in this cohort may be better achieved through a more thorough assessment of the value of surgery in these cases rather than seeking to further restrict the availability of pholcodine. The MCC minutes provide no indication that consideration of other available options, such as increasing the rigour of risk: benefit assessment for performing surgery, could more effectively mitigate the risks of surgery in general than the reclassification of medicines.

2. Anaphylaxis

The Rocuronium bromide datasheet reports anaphylaxis as very rare (<1:10,000)[iii].
The ANZCA submission claims "anaphylaxis is the leading cause of direct anaesthesia-related mortality in New Zealand and Australia, causing more deaths than airway failures, aspiration, or cardiac arrest." As anaphylaxis has been identified as the adverse event of concern, this statement deserves scrutiny, which is not apparent from the MCC minutes.

Of the 22 deaths reported in the 2012-2014 ANZCA report, where it is reasonably certain that the death was caused by anaesthesia or under the control of the anaesthetist, there were seven deaths (32%) from anaphylaxis due to drugs administered by the anaesthetist, six (27%) involved pulmonary aspiration, six (27%) involved cardiac arrest and two (9%) each for stroke and airway related deaths. The results suggest *there is no significant difference in the frequency of death by anaphylaxis compared to pulmonary aspiration or cardiac arrest*. Thus to claim anaphylaxis as the 'leading cause of death' is to present anaphylaxis, and through inference issues with pholcodine, as a greater safety concern than deaths by other causes, when the ANZCA data do not support the 'leading cause' claim.

The ANZCA submission also refers to some NZ data, which has not been made available for review, regarding 62 reports of NMBA anaphylaxis submitted to CARM between January 2017 and June 2019, in which laboratory testing of pholcodine specific IgE was measured in 37 (60%) samples from cases of NMBA anaphylaxis. ANZCA report that pholcodine specific IgE was measured in 37 (60%) of cases and found to be elevated in 20 (54%) of cases. Given no other information is reported, the relevance or significance of this information is unclear but its inclusion in the ANZCA submission suggests the intent is to support the proposition that pholcodine consumption sensitises users to quaternary ammonium ions in NMBAs and thus access to pholcodine should be restricted. Without context, no conclusions can be drawn from these data and thus they provide no credible support to justify the restriction of pholcodine.

Given the 11.40 million individual episodes of anaesthesia care, seven deaths attributed to anaphylaxis is very small; furthermore, four of these deaths were in obese patients and one had cardiac disease. These results provide no indication of the role pholcodine may have had in contributing to the anaphylaxis deaths.

When considering the overall safety of anaesthesia and the incidence of anaphylaxis, it becomes apparent that any contribution pholcodine may have to the outcome is circumstantial or speculative. The high degree of safety already associated with anaesthesia and the very rare occurrence of anaphylaxis during anaesthesia strongly suggest that further limiting the availability of pholcodine is unlikely to have any significant impact on anaesthesia outcomes.

Beyond noting that "anaphylaxis is rare and NMBA anaphylaxis is rarer again", the MCC minutes give no indication that they have considered the extremely rare occurrence of these anaphylactic events within the context of the surgical setting, and the potential contribution of pholcodine in this context. No evidence was presented that pholcodine consumption contributed to any of these NMBA anaphylaxis outcomes.

Objection 2

• the MCC did not consider all the benefits

According to the MCC minutes, the Committee agrees that consumers can appropriately self-manage coughs and cold and claims "there are alternative cough and cold products available OTC." The Committee fails to specify what these alternative OTC products, and particularly products suitable for dry cough, are. Until the up scheduling of dextromethorphan, an OTC alternative to pholcodine was available. However, this is no longer the case. Thus, the up scheduling of pholcodine to Pharmacist Only Medicine will effectively deny New Zealand consumers of any OTC remedies for the relief of dry cough. Whilst dry cough is a self-limiting condition, it is not unreasonable that consumers have access to medicines which provide relief, particularly those with a history of well-established safety and efficacy over many years, such as pholcodine.

The review conducted by iNova recognised that most efficacy studies were not well-controlled, either with active or placebo medications, and some were performed using combination products. However, all studies were conducted with appropriate populations and in relevant acute indications, which demonstrated efficacy of pholcodine, in several cases over placebo. Furthermore, there are no well-designed studies that would suggest pholcodine is *ineffective* in the approved indication. The EMA (2012) conclusions are also supportive of this assessment, concluding in their review that the "the existing data is consistent and supportive of the efficacy of pholcodine in the treatment of non-productive cough".

Pholcodine has provided relief for dry cough for over 50 years. Consumers are also unlikely to continue purchase of products for which there is no perceived benefit. This enduring use provides strong and credible evidence which supports that consumers obtain benefit from pholcodine for the relief of dry cough. The ANZCA claim that "there is a lack of efficacy for pholcodine as a cough suppressant" misrepresents the body of evidence. Their submission does not provide substantiation for this claim or for the claim that "other products for symptom relief that do not contain pholcodine would still be available to consumers." These "other products" should be identified as the availability, or lack thereof, is an important consideration in weighing up the benefits of pholcodine and its appropriate classification.

The MCC also attribute a benefit to pharmacist intervention as a justification for reclassifying pholcodine to Pharmacist Only. The New Zealand Pharmaceutical Society addresses this issue in their submission commenting that "it is unlikely that any health professional providing or prescribing pholcodine to a patient will know if they are likely to undergo surgery in the future or potentially trigger the theoretical increase in IgE which may cause anaphylaxis with NMBAs. It may be more appropriate to mitigate any risks by ensuring the patient is asked about their medicines (including pholcodine) at their pre-assessment clinical or prior to surgery."

Hence, the MCC view is not supported by the pharmacy profession expected to implement the reclassification and is another example where the Committee do not appear to have considered other risk mitigation strategies beyond product restriction.

Objection 3

• there was a breach of the appropriate process.

1. *At the 61st MCC meeting, the Committee concluded there were minimal safety concerns around pholcodine and the current [Pharmacy only] classification was appropriate. The decision-making to revoke that conclusion is not transparent and not supported by the evidence provided to the MCC.*

The Committee requested that Medsafe review the benefit:risk profile for pholcodine. Medsafe's review was referred to the MARC December 2019 meeting. The Medsafe and MARC submission recommended reclassification *despite concluding that the evidence for an association between pholcodine and NMBA anaphylaxis was insufficient*. The reasoning behind the recommendation is not transparent. Furthermore, since the Medsafe review no new studies have been published which would change the conclusion that the evidence for an association is insufficient. Therefore, the MCC decision at the 61st meeting that the classification of pholcodine as Pharmacy Only Medicine is appropriate and should remain unchanged.

2. *The MCC discussion is inconsistent with its recommendation to reclassify pholcodine to Pharmacist only medicine*. The Committee identified that:
    - New Zealand has few medicinal alternatives for dry cough, exacerbated by the up scheduling of dextromethorphan
    - The efficacy data was weak and old but that does not mean there is no need for the product as there is still consumer demand
    - Anaphylaxis is rare and NMBA anaphylaxis is rarer again. A person would have to have repeated exposure to be at risk and that exposure can come from a number of substances in the environment. The causality is unclear.
    - There is some evidence of harm, [but then referred to concerns around masking of cough rather than issues with NMBA anaphylaxis].
    - The change in classification may not mitigate the risk of anaphylaxis under anaesthetic, as the sensitisation may occur from exposure to a number of substances, but the interaction with the pharmacist may reduce the risk to the individual person.
    - There are reasons to retain the current classification, such as there are no other alternatives, that the connection with neuromuscular blocking agents is not clear due to other environmental factors, and mitigations such as taking a complete history pre-surgery.

Despite identifying a range of reasons to retain the current scheduling as Pharmacy Only Medicine as listed above, and most importantly, stating that a ***change in classification may not mitigate the risk of anaphylaxis under anaesthetic***, which is the primary reason why the classification of pholcodine is under consideration, the MCC concluded that these are not compelling reasons to retain the current classification and the risk can be best managed by moving to a restricted medicine classification.

The MCC fails to identify what would be compelling reasons to retain the current classification and how pharmacist intervention would minimise the risk of NMBA anaphylaxis during anaesthesia. If the Committee believes that a change in classification "may not mitigate the risk of anaphylaxis under anaesthetic", then there is no justification to change the classification of pholcodine as *the Committee is explicitly acknowledging that up scheduling will be ineffective.*

3. *The MCC was asked to weigh up "the unproven efficacy of pholcodine, which is widely used for symptomatic relief of self-limiting, non-serious acute cough due to upper respiratory tract infection, against an unconfirmed but suggestive association between pholcodine and an increased population risk of life-threatening anaphylaxis to NMBAs in patients undergoing surgery".*

The efficacy of pholcodine is not "unproven"; the data available supports that pholcodine is effective for the relief of dry cough. No efficacy studies have demonstrated inefficacy. The MARC review cast considerable doubt on the 'pholcodine hypothesis'. The choice of language is revealing – these are examples of language used in the review:

- "an unconfirmed but suggestive association"
- most of [the studies] were undertaken by a single research group, show an ecological association between pholcodine and NMBA-induced anaphylaxis. However, *none of the studies provide direct evidence of a causal association*."
- MARC agreed that the ecological evidence for an association between pholcodine exposure and an increased risk of anaphylaxis to NMBAs *is suggestive but not conclusive.*

The choice of language clearly demonstrates that the role of pholcodine in NMBA-induced anaphylaxis is circumstantial, the evidence to confirm an association is weak, and no evidence is available to establish causality. The level of uncertainty surrounding these observations regarding "the pholcodine hypothesis" does not justify the reclassification of pholcodine and the subsequent loss of a widely accepted safe and effective therapy for the relief of dry cough. It is reasonable that reclassification decisions should be accompanied by compelling evidence to illustrate the benefit reclassification would achieve. Such evidence has not been articulated. Decisions to restrict medicines have widespread repercussions for consumers, healthcare professionals and industry. Hence, the reasons for restriction should be clearly articulated and supported by appropriate evidence that justify the decision. This is not evident from the MCC minutes.

4. *The MCC did not consider alternatives to reclassification*

Whilst the role of the MCC is to consider the classification of medicines, reclassification is not the only option available to mitigate perceived risks associated with medicines. The NMBA data sheets make no mention of the potential, theoretical or otherwise, for cross-reactivity between pholcodine and NMBAs. This is surprising given [unsubstantiated] claims by ANZCA that this cross-reactivity "increases the risk of death and serious morbidity due to anaphylaxis to these agents." The absence of a precaution statement in the data sheets suggests the sponsor Pharmacovigilance departments are not detecting any safety signals that would warrant inclusion of a precaution in the data sheet.

Secondly, pharmacist counselling of a patient about pholcodine consumption and possible risks if the patient has surgery at some indeterminate future date, when the immediate issue is the relief of a dry cough, is unlikely to be an effective risk mitigation strategy as articulated by the NZ Pharmaceutical Society submission. If anaesthetists are concerned about pholcodine consumption, a more effective strategy would involve asking questions regarding its consumption when taking the patient's medical history prior to surgery. It is interesting that an ANZCA media release (2019)[iv], which warned Australian patients preparing for an operation that some medications they take may react with their anaesthetic, the key advice to patients did not ask them to have a list of OTC or complementary medicines in addition to prescription medicines, and did not ask patients to stop taking OTC medicines before surgery. Instead, the advice was to stop taking herbal

treatments as they may also react with anaesthetic drugs. Pholcodine is not an herbal medicine. iNova does not object to the provision of a datasheet for pholcodine as a Pharmacy Only Medicine if this could be viewed as mitigating perceived risk. However, the inclusion of any safety information regarding cross-reactivity of pholcodine and NMBAs would also reasonably be expected to be included in NMBA data sheets.

Conclusion and Recommendation

As ANZCA (2017) note "Anaesthesia in Australia and New Zealand has never been safer for our patients". This statement is supported by the evidence gathered over the 2012-2014 3-year period, when there were seven deaths attributed to anaphylaxis from a total of 11.4 million individual episodes of anaesthesia care. Of these seven deaths, four were in high risk patients. The available evidence does not support the proposition that there is a significant risk of cross-sensitisation to NMBAs and subsequent development of anaphylaxis during surgery. Given the very rare incidence of anaphylaxis and the weak evidence to support pholcodine cross-sensitisation to NMBAs, restriction of pholcodine to Pharmacist Only Medicine is unlikely to make any difference to anaesthesia outcomes, whilst denying consumers reasonable access to a safe and effective remedy for the relief of dry cough. Furthermore, the MCC recommendation to restrict pholcodine to a Pharmacist Only Medicine is inconsistent with their meeting discussion as presented in the minutes, and in particular, the view that a "change in classification may not mitigate the risk of anaphylaxis under anaesthetic." Therefore, there is no justification to reclassify pholcodine and iNova request the MCC to revoke their initial decision and retain the current classification entry for pholcodine as Pharmacy Only Medicine.

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[i] MCC (2020). Reclassification of pholcodine to restricted medicine Available online: https://medsafe.govt.nz/profs/class/Agendas/Agen64/MCC64_63_pholcodine_web.pdf

[ii] Australian and New Zealand College of Anaesthetists (2017). Safety of anaesthesia. A review of anaesthesia-related mortality reporting in Australia and New Zealand 2012-2014.

[iii] Esmeron (Rocuronium bromide) datasheet (2020). Accessed online: https://medsafe.govt.nz/profs/Datasheet/e/Esmeroninj.pdf

[iv] Australian and New Zealand College of Anaesthetists (2019). Anaesthetists warn of medication reactions during operations. Media release 16 October 2019. Available online: https://www.anzca.edu.au/resources/media-releases/2019-media-releases/anaesthetists-warn-of-medication-reactions-during.pdf

Pholcodine Reclassification – Delay to Gazettal Timing

While the preceding Objection provides a strong and valid reasoning for retaining the current Pharmacy Only Medicine classification for pholcodine, should this outcome not eventuate the date of gazettal needs careful consideration given the important implications of COVID-19.

If the committee decides to proceed with the rescheduling of pholcodine, iNova requests a delay in the gazettal of the reclassification from pharmacy-only medicine to pharmacist-only medicine to August 2021. There are special circumstances with COVID-19 that have provided pharmaceutical manufacturers and pharmacy with excess stock of cough and cold medicines. Firstly, because of the lockdown, fewer people have suffered from colds and influenza than is normal and sales are considerably lower than usual. Secondly, because of COVID-19, pharmacy has been under considerable pressure managing the demands of intermittent lockdowns and stock shortages across the range of medicines that they provide. This is likely to continue, consequently minimising their workload currently seems reasonable. Thirdly, because of COVID-19, iNova have ordered more than usual quantities of stock because of the potential for production and shipping delays, and this has increased inventory levels of cough and cold products.

iNova note that the committee indicated in their review that there is no strong evidence of pholcodine causing the proposed adverse reaction with NMBAs because of the potential for other substances to initiate this, and therefore postponement of implementation is unlikely to make any meaningful difference to surgical safety outcomes. This is not substantially different to the delays that have occurred with the codeine up scheduling to allow the market to be prepared, and it could be argued that there is less evidence of harm eventuating with pholcodine use than there is with codeine.

A one-year deferral would help pharmacists and manufacturers to manage stock in this extraordinary time and reduce the burden on pharmacists within pharmacy to manage all sales of cough preparations.

Favourable consideration by the committee of the extraordinary circumstances occurring as a direct result of the international impact of COVID-19 in the timing of activities relating to any proposed rescheduling could have a direct and meaningful impact upon pharmacies, throughout New Zealand, who are already under considerable pressure, both from a financial and workload perspective.

1st September 2020

Medicines Classification Committee
Medsafe
PO Box 5013
Wellington 6145

Dear Sir/Madam,

The Consumer Healthcare Products Association of New Zealand Incorporated (CHPNZ) wishes to lodge an objection to the Medicines Classification Committee recommendation to re-classify Pholcodine from a pharmacy only medicine to pharmacist only medicine **– Item 6.3 64th MCC Meeting**

The basis of this objection is that a "mistake in administrative law has occurred".

CHPNZ asks that the MCC review its decision having due regard to the submissions and evidence presented and recommend to the Minister of Health's representative that no change in classification is required.

The reasoning behind the request is:

Risk Evidence:
The Committee members acknowledged that the evidence showing a fatal association with anaphylaxis, neuromuscular blockers and Pholcodine was limited. This conclusion also referred to in the information and research provided to MARC relating to the "Pholcodine Hypothesis" indicated that:

> "These studies, most of which were undertaken by a single research group, show an ecological association between pholcodine and NMBA-induced anaphylaxis. However, none of the studies provide direct evidence of a causal association. Furthermore, in 2013, a French study demonstrated a 4.6-fold higher frequency of positive IgE against QAIs in hairdresser apprentices, compared with other apprentices, suggesting that exposure to other environmental QAIs may contribute to NMBA sensitisation [14].The EMA reviewed the evidence for a link between pholcodine and NMBA-induced anaphylaxis in 2011. They considered the evidence available at the time to be circumstantial, not entirely consistent, and insufficient to support the conclusion that there is a significant risk of cross-sensitisation to NMBAs."

In reviewing the data, the committee appear not to have balanced the incidence of reported anaphylactic complication in anesthesia with the total number of anesthetic procedures undertaken.

CHPNZ maintains that a mistake in administrative law occurs when, in making a decision any committee does not adequately consider the evidence and balance of evidence presented to it. When assessing the risk benefit profile of Pholcodine the scientific evidence showing risk of anaphylaxis is not conclusive and is circumstantial. This is balanced by efficacy evidence which, while also not conclusive, does not prove lack of efficacy.

We have been unable to find any evidence in New Zealand or available to us from global studies that shows that Pholcodine poses a safety risk through either excessive use or potential abuse. Note: the meeting record states "There is evidence of harm…" but does not indicate what this is or reference it. CHPNZ would appreciate clarification here, particularly if this is new data available given the 61st meeting of the Committee agreed "there was limited potential for abuse".

Decision Making Process:
The meeting record indicates that there appears to be a lack of balance when considering the eight submissions, seven of which opposed a change in scheduling compared to a single submission ANZCA (Australian and New Zealand College of Anesthetist). This submission offered poorly assessed evidence not balanced and not highlighting that of 11.4 million individual episodes of anesthetic care there were only 7 deaths attributed to anaphylaxis and that there is no evidence that Pholcodine contributed to any of these. There is certainly no new evidence presented to support a change from that which was presented to the 61st Meeting of the MCC where the conclusion then was that there were minimal safety concerns and that the current classification was appropriate.

Desired outcome as a result of up-scheduling:
The meeting record notes that the committee acknowledges that its recommendation to re-classify may not mitigate the risk of anaphylaxis under an anesthetic but the interaction with the pharmacist may reduce the risk to an individual person.

CHPNZ believes this is flawed reasoning and that the MCC clearly has misunderstood the practical pharmacist/patient interactions concerning Pharmacist-Only Medicines. It is untenable to suggest that pharmacists should quiz potential cough mixture supply requests as to whether the patient is about to undergo general anesthesia where neuromuscular blockers will be used. The responsibility to ascertain this risk is much better placed on the anesthetist, should they be administering NMBA's.

If the desired outcome is to reduce supposed risk of possible anaphylaxis then making Pholcodine a Pharmacist Only Medicine is not the answer.

Discussion outside the Scope:
The committee makes an unusual comment that most submitters opposed reclassification but then suggest a "chance to reduce the volume used by intervention of a pharmacist maybe useful". It offers no reasoning why it might be useful or how it might be useful.

The committee acknowledges it doesn't know what the sales volume of Pholcodine is and acknowledges that anaphylaxis is rare and that there is little risk of abuse or unsafe use.

CHPNZ maintains that it is not the MCC's responsibility or mandate to advise on medicines classification on the basis of affecting sales volumes and that this is a mistake in administrative law. Its mandate is to recommend medicines classification on the basis of safety and efficacy.

Consideration of Alternatives;
The meeting record does not indicate any discussion on any alternative action to re-classification; and in particular the value of a labeling change. If the safety risk is indeed solely the possibility of a sensitizing reaction with neuro-muscular blockers education on this could be achieved by the use of changed labelling.

Pre-determination:
The minutes indicate that discussion occurred on alternatives, the connection with neuromuscular blocking agents and medications such as taking a complete history pre-surgery.

It notes that these were “not considered compelling reasons to retain the current classification”.

This commentary indicates that a pre-determination by the committee to up-schedule had been made and that all evidence was being viewed as to whether there were “compelling reasons to retain”. This likely amounts to a “mistake in administrative law”.

Given the numerous apparent flaws with the decision and the decision making process, a full judicial review may be required to rule on this matter, and others raised in this objection and CHPNZ reserves the right to challenge further should the committee retain its current recommendation and that the Minister’s Representative accepts the recommendation .

CHPNZ
30th August 2020