PHARMACEUTICAL SOCIETY
of New Zealand Incorporated

11 March 2020

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 64th MEETING AGENDA Thursday 14th May 2020

Thank you for the opportunity to submit comments on the Agenda for the 64th meeting of the Medicines Classification Committee.

The Pharmaceutical Society of New Zealand Inc. (the Society) is the professional association representing over 3,700 pharmacists, from all sectors of pharmacy practice. We provide 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:

6.3 Pholcodine- reclassification from a pharmacy medicine to a restricted medicine

The Society **does not** support the application to reclassify pholcodine. The Medicines Adverse Reactions Committee (MARC) Secretariat developed a comprehensive review paper, which was discussed by MARC in December 2019 and was used to inform the Medicines Classification Committee (MCC) proposal. However, the Society have several comments that MCC may wish to consideration during their discussions.

Clinical efficacy of the product

The MARC paper has captured and evaluated a large number of studies related to pholcodine. The European Medicines Agency (EMA) state that "due to the age of the product most of the methodology used in most efficacy studies would be considered poor by modern standards".[1] This is reflected to a degree in the assessment by the MARC team.

However, EMA have recommended that existing data is also consistent and supportive of the efficacy of pholcodine in the treatment of acute non-productive cough.

The MARC paper describes outcomes of a study from 2006 (Equinozzi and Robuschi), which compared pholcodine and dextromethorphan.[2] The commentary in the MARC paper included limitations with the study and suggested that it was not possible to draw the conclusions described by the authors. However, the authors of the MARC paper have not reviewed the full published article and only accessed the abstract and published clinical trial report. Springer who published the original research are "a leading global scientific, technical and medical portfolio, providing researchers in academia, scientific institutions and corporate R&D departments with quality content through innovative information, products and services".[3] It is also likely that the original research by Equinozzi and Robuschi was peer reviewed. If the Equinozzi paper is going to be critiqued by MARC and potential limitations

assumed regarding the research, then the full primary reference should ideally be reviewed before a recommendation is made to both MARC and MCC.
Based on the current balance of the evidence available, the Society supports the EMA summary that existing data is consistent and supportive of the efficacy of pholcodine in the treatment of acute non-productive cough.

Safety of the product
Various formulations of pholcodine have been available on the New Zealand market since 1969.[4] The CARM data in the MARC report (Table 9) lists all the case reports for pholcodine since product launch.
To ensure the evidence is balanced, please can the committee remove the three cases linked to children (002896, 004285, 035772) because pholcodine is not currently used in children under 6 years old. It would also be beneficial if the committee could exclude the cases where pholcodine is not the sole ingredient, because the other suspected medicines may have caused the adverse reaction (006822, 024434, 043027, 084894, 086809).
Anaphylaxis is defined as a severe and potentially life-threatening reaction to a trigger such as an allergy.[5] The CARM data contains some reports of a potential allergic response to pholcodine but only two reports of anaphylaxis since the product was brought to market (114715, 118693). It is not clear from the information if these outcomes were confounded by the presence of other risk factors or clinical conditions. Please can the committee also consider the context and sizes of these reactions in relation all other anaphylaxis reports captured by CARM for the other pharmacy only and general sale list medicines that are currently available.

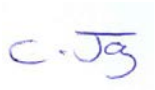
Anaphylaxis to neuromuscular blocking agents (NMBAs)
The MARC paper and MCC document provide a good summary of the information relating to anaphylaxis and NMBAs. However, the evidence presented to potentially link pholcodine and anaphylaxis to NMBAs is described as weak, is mainly ecologically defined to one population (Norway and Sweden) and later to some IgE studies in Australia. The IgE reaction has not been described wider, despite the product being freely available across multiple countries.
The authors of the MARC and MCC papers provide evidence that the "allergenic epitope responsible for IgE-mediated anaphylaxis to NMBAs is the quaternary ammonium ion which is widely available in the human environment". An alternative hypothesis to the pholcodine hypothesis is proposed which states that "sensitisation to NMBAs may therefore occur from environmental exposure to a cross-reacting substance rather than the pholcodine".
The EMA have stated that "the evidence in support of an association between pholcodine and NMBA-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".[1] Currently no additional data has been published.

Review of proposed upscheduling
It appears that there is insufficient conclusive evidence linking pholcodine and anaphylaxis to NMBAs in New Zealand. This was confirmed by MARC. Any reclassification would require the sponsor to supply a data sheet which includes adverse effects. This may be beneficial for the patient. However, with the development of the Therapeutic Products Bill this requirement could be delivered without a change of classification.
Pharmacists provide advice to patients regarding appropriate treatments, including those presentations with coughs and colds. However, 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 analphylaxis 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 clinic or prior to surgery.

This will provide real time information and also ensure all health professionals can provide optimal care for their patients.

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

Yours sincerely,



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References

1) Assessment report of Pholcodine containing medicinal products. European Medicines Agency. Feb 2012. url: https://www.ema.europa.eu/en/medicines/human/referrals/pholcodine [cited 25/2/20]

2) Equinozzi, R. and M. Robuschi, Comparative efficacy and tolerability of pholcodine and dextromethorphan in the management of patients with acute, non-productive cough : a randomized, double-blind, multicenter study. *Treat Respir Med*, 2006;**5(6)**:509-13.

3) About Springer. 2020. url: https://www.springer.com/gp/about-springer [cited 25/2/20]

4) Medsafe/Product Application Search. 31st May 2019. url: https://www.medsafe.govt.nz/regulatory/DbSearch.asp [cited 25/2/20]

5) Anaphylaxis- an overview. NHS 19th Feb 2020. url: https://www.nhs.uk/conditions/Anaphylaxis/ [cited 25/2/20]