PHARMACEUTICAL SOCIETY
of New Zealand Incorporated

23 August 2019

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

Dear Jess,

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

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

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

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

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

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

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

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

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

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

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

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

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Classification of codeine in other countries

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

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

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

Extent of usage in New Zealand

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

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

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

Electronic opioid harm monitoring system

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

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

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

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

Genetic polymorphism

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

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

Clinical outcomes

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

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

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

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

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

Benefits and risks of self-selection

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

Contraindications and precautions

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

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

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

The report notes:

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

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

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

Undesirable effects

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

Overdose and abuse/misuse potential

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

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

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

Communal harm

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

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

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

Integrated benefit-risk statement

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

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

Health equity and wellbeing

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

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

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

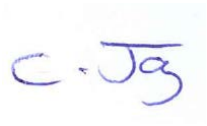
Pharmacists are trained to provide appropriate medicine information and provision of treatment for various conditions, include the management of acute pain.

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

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

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

Yours sincerely,



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