[redacted]

October 31 2018

Advisory Committee on Medicines Scheduling
Therapeutic Goods Administration

Re: Proposed amendment to scheduling of Paracetamol (modified release)

The NSW Poisons Information Centre (PIC) strongly supports the up-scheduling of modified release (MR) paracetamol preparations. The risks associated with poisoning from these products, particularly deliberate self-poisonings, far outweigh the few benefits associated with reduced frequency of dosing, from four times a day with immediate release (IR) paracetamol, to three times a day using MR paracetamol, with no evidence of increased efficacy. However, we are not convinced that a move to Schedule 3 will adequately minimise access and reduce risk. We suggest a rescheduling of all MR paracetamol to schedule 4 and IR paracetamol in packs of greater than 48 tablets to Schedule 3.

The NSW PIC provides a call centre service to NSW, Tasmania and the ACT on a near full-time basis and a shared after-hours service to the remainder of Australia. This results in approximately half of Australia's poisons-related calls being received by NSW PIC.

Research recently presented at the Toxicology and Poisons Network Australasia (TAPNA) 2018 annual scientific conference[1] shows paracetamol overdose in Australia is increasing, in both frequency and size (number of tablets). Calls to NSW PIC regarding intentional paracetamol overdose increased by 80%, 2004 to 2017. The median number of tablets ingested in each overdose has increased from 15 to 20 tablets in that period. There are also a much greater number of large overdoses, with approximately 500 ingestions of over 40 paracetamol tablets in 2017, compared to only 140 such exposures in 2004. This trend is also reflected in admissions to hospitals nationally for paracetamol poisonings, which have increased by 51% in the 16 years to 2014-15. The clinical significance of this trend is illustrated by the 449% increase in toxic liver injury in the same period. Paracetamol exposure is the most common cause of toxic liver injury in the western world[2].

Costs to the health system are impacted by these increasing admissions for paracetamol poisoning, and increase in length of stay (2.7 days in 2014-15 up from 2 days in 1998-99). Based on standard bed costs/day, this equates to a doubling in expenditure on admissions relating to paracetamol poisoning from an estimated $17M in 1998-99 to $34M in 2014-15 (adjusted for inflation).

Much of the increase in paracetamol poisonings is related to MR paracetamol, which in 2017 accounted for 12.6% of all single ingredient paracetamol exposures. The standard paracetamol concentration time nomogram cannot be used to identify patients at low risk of hepatotoxicity. In addition, the unpredictable pharmacokinetic profile of MR paracetamol results in delayed and multiple peaks so patients nearly always require the acetylcysteine antidote (compared to only around a third of IR paracetamol poisonings). They also require prolonged treatment, more

pathology services and longer admissions[3]. Thus MR paracetamol poisonings are far more expensive to treat when compared to IR paracetamol poisonings.

Analysis of most recent call data to the NSW PIC from Jan to Sept 2018 highlights the difficulties with MR paracetamol poisoning and management. Deliberate self-poisoning (DSP) with MR paracetamol is more likely to require antidote treatment with acetylcysteine, more likely to need a higher dose and a prolonged treatment. [redacted]

[redacted]

There is growing evidence from multiple sources that the rate of deliberate self-harm, including deliberate self-poisoning, is increasing amongst young people[4,5,6] and that this behaviour is starting at a younger age. NSW PIC call data shows MR paracetamol is a popular choice by young people in self-poisoning. [redacted] Access by children and adolescents to large numbers of MR paracetamol tablets needs to be minimised to address this.

We believe moving MR paracetamol to Schedule 3 will provide minimal deterrence to those looking to purchase for self harm. Previous rescheduling to Schedule 3 to reduce misuse and harm have not been successful and required further up-scheduling to schedule 4. The move of codeine to pharmacist only medicine in 2010 failed to curb the increase in codeine misuse.[7] The effects of the move of codeine to Schedule 4 earlier this year are yet to be analysed, but early indications appear favourable. More restrictive re-scheduling has been effective in the past: moving alprazolam from Schedule 4 to Schedule 8 was associated with a considerable reduction in overall use and adverse

events associated with alprazolam[8]. These factors all indicate a more restrictive approach is needed to be effective in reducing access of MR paracetamol to those likely to use it for harm.

[redacted] we feel the barrier to sale for inappropriate use needs to be greater than is currently being provided by Schedule 3. Patients using MR paracetamol appropriately for chronic pain will (or should) be under the management of a GP, and a move of MR paracetamol to Schedule 4 should not require any extra visits to the doctor for prescribing.

We acknowledge a move to prescription only might mean an increase in price of MR paracetamol for many patients, and there may be a proportion of patients who could be changed to an opiate based pain reliever due to a perception of increased effectiveness and/or value for money. This should be discouraged, and in order to avoid such events we propose reintroducing a PBS listing for MR paracetamol for those patients with an appropriate need. Any resulting increase in cost to the health system would likely be offset by the savings made as we see fewer patients admitted to hospital for management of MR paracetamol poisoning.

In the UK, reduced pack sizes of paracetamol led to a reduction in deaths resulting from paracetamol overdose[11]. Thus it is relevant to also consider pack sizes of all forms of paracetamol freely available for public purchase. There are greatly increased risks and complexities with managing massive paracetamol exposures (>35 grams) [12]. ATOM-2 study on massive paracetamol exposures showed 14% of exposures developed hepatotoxicity and 42% of these were despite standard antidote treatment being commenced within eight hours. Nearly 40% of massive exposures to paracetamol required an increased dose of acetylcysteine antidote in the first 21 hours to reduce the risk of hepatotoxicity. Restricting Schedule 2 pack sizes of IR paracetamol to 48 tablets would help to reduce the likelihood of massive paracetamol poisonings from single impulsive purchases, while having minimum impact on access to affordable OTC paracetamol.

Regards

[redacted]

Senior Specialist in Poisons Information – Toxicovigilance
NSW Poisons Information Centre

[redacted]

Clinical Director
NSW Poisons Information Centre

1. Cairns, R., & Buckley, N.A. (2018) Flavour of the decade: increasing frequency and size of paracetamol overdose reported to Australia's Largest Poisons Information Centre. In: Toxicology and Poisons Network Australasia 2018 Scientific meeting, Sydney, 2018
2. Larson AM, Polson J, Fontana RJ, *et al.*Acetaminophen-induced acute liver failure: Results of a United States multicenter, prospective study. *Hepatology* 2005;42:1364–72. doi:10.1002/hep.20948
3. Angela L. Chiew, Geoffrey K. Isbister, Colin B. Page, Katharine A. Kirby, Betty S. H. Chan & Nicholas A. Buckley (2018) Modified release paracetamol overdose: a prospective observational study (ATOM-3), Clinical Toxicology, 56:9, 810-819, DOI: 10.1080/15563650.2018.1439950
4. Perera J, Wand T, Bein KJ, Chalkley D, Ivers R, Steinbeck KS, et al. Presentations to NSW emergency departments with self-harm, suicidal ideation, or intentional poisoning, 2010-2014. Med J Aust. 2018;208(8):348–53.
5. Hiscock H, Neely RJ, Lei S, Freed G. Paediatric mental and physical health presentations to emergency departments, Victoria, 2008-15. Med J Aust. 2018;208(8):343–8.
6. Cairns R, Buckley NA. Increased self-poisoning in young Australians: Why, 2Ks? In: 15th International APAMT Scientific Conference. Singapore; 2016.
7. Cairns, R., Brown, J., & Buckley, N.A. (2016). The impact of codeine re-scheduling on misuse: a retrospective review of calls to Australia's largest poisons centre. *Addiction*, *111*(10), 1848–1853. http://doi.org/10.1111/add.13450
8. Schaffer, A. L., Buckley, N. A., Cairns, R., & Pearson, S.-A. (2016). Interrupted Time Series Analysis of the Effect of Rescheduling Alprazolam in Australia. *JAMA Internal Medicine*, *176*(8), 1223. http://doi.org/10.1001/jamainternmed.2016.2992

[redacted]

10. NSW PIC Database
11. Hawton, K., Bergen, H., Simkin, S., Dodd, S., Pocock, P., Bernal, W., Gunnel, D., Kapur, N. (2013). Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: Interrupted time series analyses. *British Medical Journal*, *346*(7895), 1–9. http://doi.org/10.1136/bmj.f403
12. Angela L. Chiew, Geoffrey K. Isbister, Katharine A. Kirby, Colin B. Page, Betty S. H. Chan & Nicholas A. Buckley (2017) Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose (ATOM-2), Clinical Toxicology, 55:10, 1055-1065, DOI: 10.1080/15563650.2017.1334915