Queensland Poisons Information Centre
Pharmacy Department, Level 2
Lady Cilento Children's Hospital
Brisbane, 4001
Queensland, Australia
www.Poisons.Info@health.qld.gov.au
31st October 2018

Dear Sir/Madam

RE: Amendment to the scheduling of Modified Release (MR) Paracetamol

I am writing on behalf of the Queensland Poison Information Centre (QPIC) to strongly support the scheduling change to MR paracetamol. Recent research into overdose with MR paracetamol and review of the QPIC data supports our belief that restricting MR paracetamol to the general public is important for patient safety. Results from an Australian research paper Australian Toxicology Monitoring Study "ATOM-3" into overdoses with MR paracetamol has shown it be less responsive to standard antidote treatment regimes, with higher rates of morbidity and longer hospital length of stay[1]. This leads to a significant increase in the financial burden on our healthcare system. Our data also shows that teenage girls represent a significant proportion of patients that are attempting overdoses on these tablets and that the unrestricted accessibility to this agent is exposing them to an unprecedented level of harm.

The following information is provided:

1. Analysis of QPIC data
2. Recent cases which highlight the concerns with MR paracetamol (September 2018)
3. Research summarising the issues with MR paracetamol in poisoning

1. Analysis of QPIC data

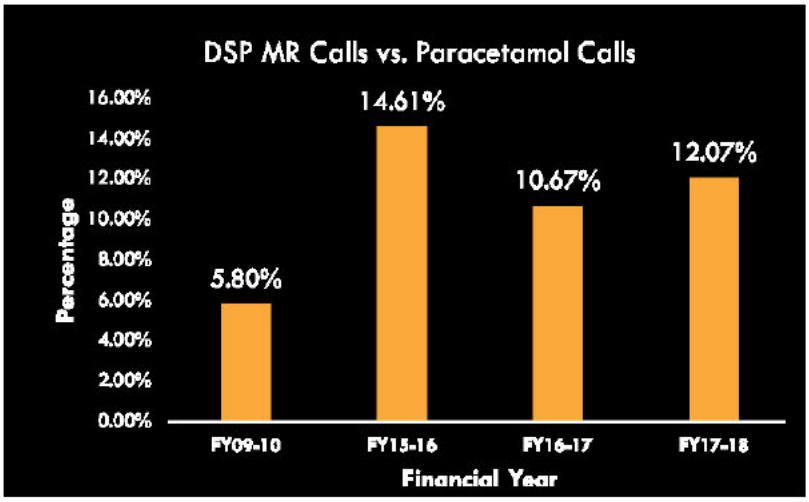
Calls to Queensland Poisons Information Centre regarding deliberate self-poisonings (DSP) with

Financial Year	Total Paracetamol calls *note: minus recalls	Total MR Paracetamol calls *note: minus recalls	Total MR Paracetamol calls with ingestion >30g
2009-2010	138	8	0
2015-2016	308	45	8
2016-2017	375	40	18
2017-2018	381	46	11

single ingredient paracetamol products

*recalls are additional calls to QPIC for advice about the same case

Graph showing percentage of DSP with MR Paracetamol vs Total Paracetamol calls



- Between FY 2016 and FY2018, deliberate self-poisonings from MR paracetamol accounted for approx. 12 % (average) of all *single ingredient paracetamol* calls to QPIC.
- From FY 2010 to FY 2018 the total number of paracetamol MR overdose calls increased from 8 per year to 46 per year and marks *a **475%*** increase over the 9-year period.
- Marked increase of ingestions greater than 30g which are associated with higher risk of liver toxicity.
- The majority of ingestions (55-63%) were in the adult age range of 20-74 years (average age approx. 30 years) from FY 2015 to FY 2018.
- Approximately 30% of the calls are regarding deliberate self - harm in teenagers between 15-19 years
- There has been a clear shift towards females overdosing with MR paracetamol with 80% female and 20% male in FY 2018 compared with FY 2010 which showed a 50/50 split
- A significant proportion of MR paracetamol calls have required specialist toxicologist consultation and advice, highlighting the complexity of managing these cases.

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Issues of concern:
The issues highlighted by this cluster of paracetamol modified release overdoses include:

- Copycat approach amongst the teenage population.
- Easy accessibility to this agent.
- Lack of education about the potential toxicity of MR paracetamol.
- Prolonged length of hospitalisation, prolonged treatment and complexities such as hospital transfer which is a burden to our state-wide hospital and health system.

3. Research summarising the issues with MR paracetamol in poisoning

- Modified release paracetamol is available as 665mg tablets containing 69% modified release and 31% immediate release – designed to release paracetamol slower over a longer period.
- Absorption kinetics in acute overdose is unpredictable with a prolonged delay in serum peak levels as well as multiple paracetamol concentration peaks following ingestion [1,3]
- Recent Australian research from the Australian Toxicology Monitoring Study (ATOM) has shown:

- The treatment regimes used for immediate release (IR) paracetamol overdoses did not appear effective for overdoses with MR paracetamol formulations. Treatments including activated charcoal and higher doses of the antidote N-Acetyl Cysteine (NAC) still resulted in higher rates of liver injury and hospital length of stay[1].
- Despite early treatment with NAC – within 8hours of an MR paracetamol ingestion, some patients still developed liver injury[1].

- Clinically, MR paracetamol has been found to have little benefit compared to IR paracetamol. The benefits are limited to a reduced dosing regime of three times a day with MR compared to four times daily for immediate release.[4,5]
- Massive ingestions (>30g) of paracetamol are associated with increased risk of hepatotoxicity[2]. MR paracetamol is available online or at a local chemist as a box of 96 tablets so only half a box (48 tablets) is required to reach this toxic threshold. A current online special is advertised as $3.99 for 96 caplets (Oct 2018)
- Recent international regulatory actions have resulted in MR paracetamol products being suspended from sale in Europe in 2017[6] and following this, also recently rescheduled in New Zealand to pharmacist only restricted medicine.

The recommendation of the Queensland Poison Information Centre to make modified release paracetamol products prescription-only is informed by research, and would align Australia with other countries across Europe and New Zealand in restricting access to the public. Currently, the unfettered access to MR paracetamol 665mg, in a pack size of 96 tablets, is placing patients who overdose at an unacceptable risk. The current antidote treatment regime appears to be less effective in overdose with MR paracetamol compared with IR paracetamol in preventing liver toxicity. Furthermore, the MR products offer no meaningful therapeutic advantage over the IR paracetamol product. Until further research can identify an adequate treatment regime for overdose of MR paracetamol, it is imperative for patient safety that this medication be restricted to S4 prescription only medicine.

Regards

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References

1. 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, DOI: 10.1080/15563650.2018.1439950

2. Chiew AL, Fountain JS, Graudins A, et al. Summary statement. New guidelines for the management of paracetamol poisoning in Australia and New Zealand. Med J Aust 2015; 203: 215-218.

3. Salmonson, H., Sjoberg, G. & Brogren, J. 2018, "The standard treatment protocol for paracetamol poisoning may be inadequate following overdose with modified release formulation: a pharmacokinetic and clinical analysis of 53 cases", *Clinical Toxicology,* vol. 56, no. 1, pp. 63-68.

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5. Bacon, T.H., Hole, J.G., North, M. & Burnett, I. 2002, "Analgesic efficacy of sustained release paracetamol in patients with osteoarthritis of the knee", *British Journal of Clinical Pharmacology,* vol. 53, no. 6, pp. 629-636

6. European Medicines Agency. Modified-release paracetamol-containing products to be suspended from EU market. Recommendation endorsed due to the difficulty in managing overdose. 2017. (cited October 2018)