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Response to:

Consultation: Referral of proposed amendment to the current Poisons Standard to the meeting of the ACMS, March 2019

A proposed amendment initiated by a delegate of the Secretary of the Department of Health regarding the rescheduling of paracetamol (modified release) from Schedule 2 (Pharmacy Medicine) to Schedule 3 (Pharmacist Only Medicine)

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Executive Summary

Modified release (MR) tablets, containing 665 mg of paracetamol, have been approved and marketed as a pharmacy medicine (Schedule 2 medicine) in Australia since 2001. A current proposal is being considered to:

- Correct the terminology in the Poisons Standard from 'slow release' paracetamol to 'modified release' paracetamol.
- Reschedule modified release paracetamol from Schedule 2 to Schedule 3.

GSKCH has no objections to the proposal to correct the terminology of MR paracetamol. However, recognizing that any change in scheduling status should be based on sound evidence that (i) the concerns are based on accurate evidence and (ii) that scheduling changes are the only mechanism for addressing these concerns.

GSKCH opposes the proposal for the rescheduling of MR paracetamol.

The TGA/ACMS has proposed six reasons for considering the rescheduling of MR paracetamol.

1. The TGA has conducted a review of the safety of MR paracetamol in Australia, and sought the advice of the Advisory Committee on Medicines, following a decision by the European Medicines Agency (EMA) to suspend marketing of MR paracetamol products in the European Union (EU). The EMA's decision was based on an increased risk of death or serious liver injury in people who overdose either deliberately or accidentally on MR paracetamol compared to immediate release (IR) paracetamol. The increased risk arose because of the unpredictable levels and duration of paracetamol in the blood following an overdose with MR paracetamol.

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- During the 17-year period that MR paracetamol has been available in Australia, the TGA Adverse Drug reaction system (ADRS) database lists 53 adverse event reports relating to MR paracetamol and 4 deaths, of which causality linked to MR paracetamol was deemed possible in only one case.
- There has been only one death reported in Australia in association with paracetamol MR (an 87-year old man who died from respiratory failure secondary to aspiration 30 h post-ingestion of MR paracetamol) (Chiew et al 2018).
- There have been no deaths in patients who have developed hepatotoxicity subsequent to MR paracetamol overdose (Graudins 2014, Chiew et al 2018), and the number of toxic cases is proportionally lower compared to Sweden (who initiated the EMA PRAC referral).
- A review of published literature suggests that the nature, severity of the events, and outcome in overdose experiences with MR and IR formulations of paracetamol are not different.

- There is no signal to indicate an increased risk with the use of MR paracetamol in Australia.

2. The antidote used to treat paracetamol overdose is short-acting but MR paracetamol products may continue to increase blood levels of paracetamol after the effects of the antidote have worn off. In many cases doctors treating an overdose are not aware which formulation of paracetamol has been taken. The higher strength of MR paracetamol and the large pack size increase the risks. An Australian study has confirmed that MR paracetamol is less safe when involved in an overdose.

- Australian and New Zealand paracetamol overdose guidelines state that antidote treatment (with acetylcysteine) should be given to all patients who have ingested an MR paracetamol dose >10 g (Chiew et al 2015). The effectiveness of this dose-based approach to identifying patients in whom to initiate acetylcysteine is established.
- By contrast, Swedish guidelines state that antidote treatment (with acetylcysteine) should be given based on where a patient's blood level of paracetamol is relative to a line on a chart (called a nomogram).
- A series of analyses has been undertaken, using data from GSK worldwide safety database, which establish that the Australian and New Zealand overdose treatment guideline protocols are more effective than those previously used in Sweden.
- Data from a [redacted] and from the published Chiew 2018 analysis, alongside the very low reported incidence of overdose cases with MR paracetamol, suggest that the current Australian and New Zealand overdose treatment guidelines are effective in minimising the risk of hepatotoxicity following overdose with MR paracetamol.
- There is a recognised need for adaptation to ensure optimal treatment in the very small portion of patients who take a very large (≥40 g) overdose. Such a large overdose is unlikely to occur as an accidental ingestion.
- Currently available data establish that in a year there are approximately 800 calls to the NSW PIC relating MR paracetamol (for any reason) and this has been investigated and extrapolated by TGA to reflect approximately 262 cases of toxic overdose (>10 g) with MR paracetamol in 2016 in all of Australia. Equating this data to the sales of MR paracetamol in 2016 (1,171,103,753 tablets):
    - There were 0.698 PIC inquiries for any reasons per 1 million tablets sold.
    - There were 0.223 cases of toxic overdose per 1 million tablets sold.

  This is lower than that observed in all other countries analysed, despite sales being significantly higher in Australia than in other markets. The data shows that the there is a more than 5-fold higher incidence of inquires relating to MR paracetamol in Sweden than in Australia, despite higher sales and less restrictive access in Australia. Both Denmark and New Zealand also display a significant difference to Sweden, where there was a 4-fold higher incidence of **3.614 inquiries per 1 million modified-release paracetamol tablets sold** compared to either of these two countries.

- Accessibility to means is considered to be a risk factor for self-harm. However, the data from Australia, Denmark and New Zealand provide compelling evidence that in countries where best practice overdose guidelines are established differences in medicines scheduling status did not appear to have had impact on the incidence of overdose. This negates the proposition that rescheduling may pre-emptively prevent higher incidence rates that have been observed elsewhere. Further it provides support to retain the current scheduling given that there is an extremely low incidence of incidence of overdose events relating to the consumption of MR paracetamol given the large number of dosage units that are sold in Australia. Restricting availability, and providing additional healthcare professional intervention, will not provide any significant additional benefit to this safety profile.
- The rescheduling of MR paracetamol therefore disadvantages the many people who are already responsibly using this product to protect the small minority who opt to use it for deliberate self-harm.

3. MR paracetamol appears to provide little benefit over standard immediate release IR paracetamol other than less frequent dosing.

- The role of MR paracetamol in the management of osteoarthritis is clearly established. Robust information support that the three-times daily dosing schedule afforded by MR paracetamol offers considerable benefit over IR paracetamol in this particular context.
- Three-times daily dosing is the key driver behind the strong benefit attributes of MR paracetamol versus IR paracetamol, which include:
    - Reduced pill burden and associated improvements in patient adherence and persistence with prescribed therapy (Ortiz et al 2016) (Benson et al 2009)
    - Better ability to achieve steady state serum paracetamol concentrations, which facilitates around-the-clock analgesia, reduced the potential for breakthrough pain and improved overnight pain control (Bacon et al, 2002).
    - Less need for escalation to stronger (opioid) analgesics (Ortiz et al 2016).
- The recently released Royal Australian College of General Practitioners (RACGP) guideline for the management of hip and knee OA (RACGP, 2018) suggest that, "*Nonsteroidal anti-inflammatory drugs (NSAIDs; eg ibuprofen), taken orally at low doses for short periods are recommended for some people with knee and/or hip OA. Monitoring for possible adverse effects of the drugs is necessary*."
- MR paracetamol is a useful treatment alternative for patients who are unable to take NSAIDs due to tolerability or contraindications, without the need to adhere to the four-times daily dosing schedule required with standard (immediate release, IR) paracetamol.
- Having MR paracetamol available under the same Pharmacy Medicine schedule as NSAIDs is paramount to maintaining appropriate consumer self-selection access in the pharmacy.

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4. The complex and unpredictable pharmacokinetic profile of MR paracetamol following an overdose means that the continued availability of MR paracetamol in pack sizes of 96 caplets as a Schedule 2 medicine poses an unacceptable to risk to the Australian population.

- In November 2017, ibuprofen underwent a scheduling review in response to an application that they be rescheduled from Schedule 2 to Schedule 3, as is now proposed for MR paracetamol.
- Ibuprofen is regarded as being generally benign in overdose. There are no established guidelines for ibuprofen overdose management in Australia.
- Analysis of the TGA Database of Adverse Event Notifications (DAEN) shows:
    - More "*Injury, poisoning and procedural complications*" case reports overall with ibuprofen (74 vs 49), more cases with a single suspected medicine (36 vs 32) and 7-fold more cases of death (15 vs 2) than with MR paracetamol.
    - A higher frequency of overdose cases with MR paracetamol than with ibuprofen (40 vs 24).
    - A lower frequency of overdose-related deaths with MR paracetamol than with ibuprofen (0 vs 3).
- Based on this, MR paracetamol has a similar, if not better, safety profile in overdose than does ibuprofen.
- Restricting access to MR paracetamol presents consumers with an unnecessary barrier to access this product, despite data supporting it to be as safe in use as ibuprofen.

5. International regulators including the European Medicines Agency and New Zealand's Medsafe have taken action on this issue with the EMA suspending the sale of MR paracetamol in EU member countries altogether.

- Unlike in Sweden, the Danish and the Australian/New Zealand paracetamol overdose treatment protocols are based on a paracetamol dose principal.
- On the basis of these established guidelines, the Danish Medicines Authority has lifted the suspension and so re-instated the product licences permitting the sale of modified-release paracetamol.
- Medsafe has recently accepted that the MCC did not consider all the safety and benefit issues correctly, the reclassification of MR paracetamol in New Zealand will therefore be reconsidered at the MCC's 61st meeting.
- The process to lift the marketing suspension on MR paracetamol is currently on-going in several other European countries, including Finland and Belgium.
- Key elements of this process include utilisation of best practices in overdose guidance and the introduction of additional risk mitigation strategies such as suitable paracetamol overdose guidelines, blister packaging and consumer education.
- All of these risk mitigation strategies have been in place in Australia for over 17 years.

- More recently, Labelling Order 92 introduced by TGA for OTC medicines (TGO92) makes important information about medicines easier to find. The changes will further help Australians make more informed choices about their medicines and use them more safely.
- In Australia, GSKCH provides extensive and easily accessible educational material to both healthcare professionals and consumers that clearly communicate the differences between MR and IR paracetamol.

6. Up-scheduling MR paracetamol to Schedule 3 will provide an opportunity for pharmacists to counsel patients on the importance of not exceeding a dose of 6 tablets per day, whilst still preserving OTC access to these products.

- The situation in Sweden is different to that in other markets, including Australia.
- Unlike in Sweden, high incidence rates of overdose with MR paracetamol have not been observed in other markets.
- Using the number of calls to Poisons Information Centres as a proxy for all overdose cases (regardless of intent) and based on data available, in 2016-17 there was an average of:
    - 0.698 inquiries per 1 million modified-release paracetamol tablets sold in Australia where modified-release paracetamol is a Schedule 2 Medicine
    - 0.903 inquiries per 1 million modified-release paracetamol tablets sold in New Zealand where modified-release paracetamol is a Pharmacy Only (Schedule 2 equivalent) Medicine,
    - 0.830 inquiries per 1 million modified-release paracetamol tablets sold in Denmark where modified-release paracetamol is a Prescription Only Medicine,
    - 3.614 inquiries per 1 million modified-release paracetamol tablets sold in Sweden where modified-release paracetamol is a Prescription Only Medicine.
- Data from Australia, Denmark and New Zealand provide compelling evidence that in countries where best practice overdose guidelines are established differences in medicines scheduling status does not have an impact on the incidence of overdose.
- These points negate the proposition that rescheduling may pre-emptively prevent higher incidence rates that have been observed elsewhere.

In conclusion:

- **The overwhelming majority of patients who use MR paracetamol in Australia do so responsibly and with little risk of accidental overdose.**
- **Current risk mitigation measures are adequate.**
- **There are no data to suggest that rescheduling MR paracetamol from its current Schedule 2 status to Schedule 3 will improve on this already favourable position.**

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CONTENTS

Introduction

1.1 Background

Modified release (MR) paracetamol tablets, containing 665 mg of paracetamol, have been approved and marketed as a Pharmacy Medicine (Schedule 2) in Australia since 2001. There are currently 26 MR paracetamol products entered in the Australian Register of Therapeutic Goods (ARTG). This medicine is principally indicated for the "*Relief of persistent pain associated with osteoarthritis*", for which it is predominantly supplied in packs containing 96 tablets.

MR paracetamol provides the benefits of standard paracetamol with the added convenience of a three times daily dosing regimen (Bacon 2001). The clinical rationale for using an MR paracetamol formulation is to provide a product with an 8-hour duration of action to facilitate adherence and improved outcomes in conditions such as osteoarthritis (OA) that require on-going management (Ortiz et al 2016). Ortiz et al have reported that tablet burden and dose frequency are barriers to appropriate use in patients who are prescribed standard (immediate release, IR) paracetamol (Ortiz et al 2016). Data from a longitudinal analysis of paracetamol prescribing in Australia over a 2-year period has proven that patient persistence with MR paracetamol therapy is significantly higher than is that with IR paracetamol, with subsequent impact on less need for escalation up the WHO pain ladder to the use of stronger pain medicines (Ortiz et al 2016).

In September 2018, the Therapeutic Goods Administration (TGA) asked the Advisory Committee on Medicines Scheduling (ACMS) to consider whether MR paracetamol should become a Schedule 3/Pharmacist Only medicine. This request has been prompted by a TGA review of the safety of MR paracetamol in Australia, and subsequent advice from the Advisory Committee on Medicines (ACM), following a decision by the European Medicines Agency (EMA) to suspend marketing of MR paracetamol products in the European Union.

The decision to suspend MR paracetamol products in Europe followed a complex Article 31 Referral procedure in the European Economic Area (EEA), which centred on concerns regarding MR paracetamol overdose in Sweden, where high rates of overdose and complexities managing such paracetamol overdose cases had been identified as a safety issue.

Overdose guidelines designed to specifically address the considerations required with MR paracetamol have been in place in Australia since its first launch in this market; initially as an unpublished guideline and later as publications in the *Medical Journal of Australia* (Chiew et al, 2015). During the 17-year period that MR paracetamol has been available in Australia, the TGA Adverse Drug reaction system (ADRS) database lists 53 adverse event reports relating to MR paracetamol and 4 deaths, of which causality linked to MR paracetamol was deemed possible in only one case (TGA Rescheduling Application, Page 24).

When available in a self-select environment (e.g. Schedule 2/Pharmacy Medicine), there are robust data to support that MR paracetamol has an overall acceptable benefit-risk profile when used to manage mild to moderate pain associated with osteoarthritis. Risk minimisation to prevent accidental overdose and impulsive deliberate overdose with MR

paracetamol is adequate and will not be meaningfully altered by changing its scheduling status to the more restrictive Schedule 3/Pharmacist Only medicine.

1.2 Summary of reasons for proposal

The proposal being considered contains two elements:

1. Correct the terminology in the Poisons Standard from 'slow release' paracetamol to 'modified release' paracetamol.
2. Reschedule modified release paracetamol from Schedule 2 to Schedule 3.

The reasons for these proposals have been summarised by the TGA in its invitation for public submissions as follows:*

1. **The current term '*slow release*' in the Poisons Standard does not correctly describe the pharmacological action of this formulation of paracetamol and '*modified release*' is the correct terminology and is used in all the product information.**
2. **The TGA has conducted a review of the safety of MR paracetamol in Australia, and sought the advice of the Advisory Committee on Medicines, following a decision by the European Medicines Agency (EMA) to suspend marketing of MR paracetamol products in the European Union (EU). The EMA's decision was based on an increased risk of death or serious liver injury in people who overdose either deliberately or accidentally on MR paracetamol compared to immediate release (IR) paracetamol. The increased risk arose because of the unpredictable levels and duration of paracetamol in the blood following an overdose with MR paracetamol.**
3. **The antidote used to treat paracetamol overdose is short-acting but MR paracetamol products may continue to increase blood levels of paracetamol after the effects of the antidote have worn off. In many cases doctors treating an overdose are not aware which formulation of paracetamol has been taken. The higher strength of MR paracetamol and the large pack size increase the risks. An Australian study has confirmed that MR paracetamol is less safe when involved in an overdose.**
4. **MR paracetamol appears to provide little benefit over standard immediate release IR paracetamol other than less frequent dosing.**
5. **The complex and unpredictable pharmacokinetic profile of MR paracetamol following an overdose means that the continued availability of MR**

* Sourced from: "Consultation: Referral of proposed amendment to the current Poisons Standard to the meeting of the ACMS, March 2019. Invitation for public submissions: Paracetamol (modified release). Available from: https://www.tga.gov.au/consultation-invitation/consultation-referral-proposed-amendment-current-poisons-standard-meeting-acms-march-2019

paracetamol in pack sizes of 96 caplets as a Schedule 2 medicine poses an unacceptable to risk to the Australian population.

6. **International regulators including the European Medicines Agency and New Zealand's Medsafe have taken action on this issue with the EMA suspending the sale of MR paracetamol in EU member countries altogether.**
7. **Up-scheduling MR paracetamol to Schedule 3 will provide an opportunity for pharmacists to counsel patients on the importance of not exceeding a dose of 6 tablets per day, whilst still preserving OTC access to these products.**

1.3 Key considerations addressed in this submission

The key considerations being addressed in this submission are therefore as follows:

Proposal	Submission sections
Amend the terminology in the Poisons Standard from 'slow release' paracetamol to 'modified release' paracetamol	Terminology used in the Poisons Standard
Reschedule modified release paracetamol from Schedule 2 to Schedule 3.	Clinical benefits of three-times daily dosing with MR paracetamol Safety profile of MR paracetamol MR paracetamol risk:benefit profile in OA Management of MR paracetamol overdose MR paracetamol in different markets – availability and overdose risk Implications of the pharmacokinetics of MR paracetamol on overdose Adequacy of Australian overdose management guidelines Risk-benefit profile of MR as a schedule 2 medicine Adequacy of risk minimisation strategies

[redacted]

Proposal 1:
Amend the terminology in the Poisons Standard from 'slow release' paracetamol to 'modified release' paracetamol

2 Terminology used in the Poisons Standard

Currently all non-standard solid dose formulations of paracetamol in Australia are referred to as "slow release". The submission seeks to amend the terminology in the Poisons Standard to more accurately reflect the formulation of these products and thus change the terminology to "modified release".

GSKCH, as the license holder of the innovator MR paracetamol product, confirms that the bilayer construction and pharmacokinetic profile of its formulation complies with this definition and therefore supports this proposal. GSKCH supports this effort to clarify the product definition, acknowledging that doing so may aid in promoting greater harmonisation between MR paracetamol products and therefore positively impact patient outcomes.

Proposal 2:
Up-schedule modified release tablets paracetamol from Schedule 2 to Schedule 3

3 Clinical benefits of three-times daily dosing with MR paracetamol

From the TGA Rescheduling Application (reference):[†]
"MR paracetamol would appear to provide little benefit over standard IR paracetamol other than less frequent dosing."

The above description of the benefit of MR paracetamol falls far short of explaining the multiple positive impacts that less frequent dosing can have when used to manage mild-to-moderate, chronic pain states, such as osteoarthritis. Robust information, provided below, support that the three-times daily dosing schedule afforded by MR paracetamol

† Sourced from: "Consultation: Referral of proposed amendment to the current Poisons Standard to the meeting of the ACMS, March 2019. Invitation for public submissions: Paracetamol (modified release). Available from: https://www.tga.gov.au/consultation-invitation/consultation-referral-proposed-amendment-current-poisons-standard-meeting-acms-march-2019

offers considerable benefit over immediate-release paracetamol (IR paracetamol) in this particular context.

Three-times daily dosing is the key driver behind the strong benefit attributes of MR paracetamol versus IR paracetamol, which include:

- Reduced pill burden and associated improvements in patient adherence and persistence with prescribed therapy (Ortiz et al 2016).
- Better ability to achieve steady state serum paracetamol concentrations, which facilitates around-the-clock analgesia, reduced the potential for breakthrough pain and improved overnight pain control (Bacon et al, 2002).
- Less need for escalation to stronger (opioid) analgesics (Ortiz et al 2016).

3.1 MR paracetamol clinical efficacy overview

A literature search‡ has identified a total of 20 studies that report use of any MR paracetamol formulation, nine of which have evaluated MR paracetamol formulations in OA (Table 1). There have been five clinical studies with the GSKCH 665 mg MR paracetamol tablets in in OA pain (Bacon et al, 2002; Yelland et al, 2007; Benson et al, 2009; Chin et al, 2012; [redacted]). As indicated in Table 1, three of these five these OA pain studies were conducted in Australia.

Table 1. Clinical studies with modified release paracetamol formulations – acute pain states in shaded rows.

OA	**GSKCH MR formulation (665 mg modified release paracetamol tablets)**	(Bacon et al, 2002)* (Yelland et al, 2007)* (Benson et al, 2009)* (Chin et al, 2012) [redacted]
	Other MR formulations	(Schnitzer et al, 2009) (Prior et al, 2014) (Yaligod et al, 2014) (Altman et al, 2007)

* Studies conducted in Australia.

‡ Literature search strategy:
Published literature was searched using the following search strategy: (("acetaminophen"[MeSH Terms] OR "acetaminophen"[All Fields]) AND efficacy [All Fields] AND ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields])) AND (modified [All Fields] OR sustained [All Fields] OR extended [All Fields]) AND Clinical Trial [ptyp].
In addition, hand searching of reference lists of identified publications was carried out as was review of the data in major regulatory submissions for non-GSK MR paracetamol formulations (e.g. Tylenol Extend NDA to the FDA).

3.1.1 MR paracetamol versus IR paracetamol

Three clinical trials in patients with OA provide a direct efficacy comparison between MR and IR paracetamol in pain management (Table 2). A key finding is that the MR paracetamol formulation provides a longer duration of pain relief than does standard IR paracetamol, enabling three-times daily dosing.

Table 2. Outcome of studies directly comparing MR versus IR paracetamol in patients with OA

Studies	Outcome
Bacon, 2002(Bacon et al 2002)	MR non-inferior to IR for global assessment of pain relief on day 8. No significant differences in other parameters (pain on waking, pain at rest, times woken during night, morning stiffness)
Benson, 2009(Benson et al 2009)	Significant preference in favour of MR paracetamol. No significant difference in compliance or sleep disturbance.
Yaligod, 2014(Yaligod et al 2014)	Open-label study with very low paracetamol doses in each arm (MR 1300mg/day vs IR 1500mg/day) Reduction in pain intensity significant vs IR paracetamol at weeks 2, 4 and 6 ($p<0.001$). Significant differences in daily living and quality of life.

3.1.2 Benefits of three-times daily dosing

It is recognised that pain states that require ongoing analgesia, such as the pain of OA, are more effectively managed by analgesics dosed in a time contingent rather than in a pain contingent manner, on the basis that time contingent dosing is associated with more stable drug levels and improved pain relief.(NPS 2006) However, poor compliance with dosing schedules, particularly when treatment is prescribed in a time contingent manner, can lead patients to perceive that their treatment is ineffective.(NPS 2006) As a result, the possibility that patients require additional or alternative analgesics is increased.

The goal for management of OA pain is to balance the efficacy, safety and cost-effectiveness of treatment. In recognition that daily dose frequency of standard paracetamol is a barrier to patient compliance and perceived treatment effectiveness,(Claxton et al 2001, Milder et al 2011) MR paracetamol was developed to provide all the benefit of an IR formulation with the advantage of sustained analgesia to enable a reduction in daily dose frequency. The rapidity of onset and stability of therapeutically active drug plasma concentrations are critical features of its utility in the treatment of OA pain.

Poor patient compliance with medications for OA pain has been demonstrated in a number of studies.(Punchak et al 2000, Carr 2001, Blamey et al 2009) The barriers to

compliance are complex and varied and can be unintentional or intentional.(Lehane et al 2007, Laba et al 2013) One important barrier is daily dose frequency, which is inversely related to compliance across a variety of therapeutic areas.(Claxton et al 2001, Richter et al 2003) Evaluation of data from 76 studies revealed that mean dose-taking compliance was 65% (± 16%) with three doses per day compared to 51% (±20%) with four doses per day.(Claxton et al 2001) An in-depth interview-based study of 15 OA patients highlights the complex relationship between daily dose frequency, patient compliance and treatment effectiveness.(Milder et al 2011) Thirteen patients were receiving paracetamol treatment at the time of interview, but only two were taking the recommended maximum daily dose. High pill load was the main cause of non-compliance.

A preference study involving 199 patients with pain from OA of the knee provides evidence that reducing daily dose frequency of paracetamol may improve patient compliance.(Benson et al 2009) In this multi-centre, randomized, open-label, two-way crossover phase IV study, patients took either the GSK MR paracetamol formulation (two 665 mg tablets every 6-8 hours, three times daily) or standard IR paracetamol (two 500mg tablets every 4-6 hours four times daily) for two weeks and were then switched to the other treatment for two weeks. All preference endpoint comparisons overwhelmingly favoured the modified-release treatment:

- 75.9% of patients stated a preference for a three times daily treatment regimen compared with 17.1% stating a preference for a four times daily treatment regimen and 7% stating no preference.
- 79% of patients agreed that the three times daily routine would be easier to comply with than the four times daily routine if to be taken regularly.
- 57% of patients stated an overall preference for the modified-release treatment compared with 27.1% preferring the standard treatment and 15.6% stating no preference.

This study also demonstrated greater improvements with MR paracetamol in overall knee joint pain and pain when waking up, compared with standard paracetamol. Given that the treatment adherence rates were similar in this study, with both regimens providing approximately 4 g of paracetamol per day, the investigators have suggested that MR paracetamol may provide a more consistent therapeutic plasma concentration of paracetamol, which is favourable for people who require long-term analgesia.(Benson et al 2009) The MR paracetamol treatment regimen provided an advantage in pain relief despite equivalent delivery of total daily paracetamol dose; the results, are however, limited by the short duration of the trial.

The study demonstrated that the MR formulation was preferred in a 2:1 ratio, providing better overall joint pain relief, which resulted in higher levels of satisfaction in subjects with osteoarthritis of the knee and has therefore potential to improve patient compliance and, therefore, pain control (Benson et al 2009).

3.2 Therapeutic place of MR paracetamol

After non-pharmacological approaches, the most common action taken to manage osteoarthritic pain is the use of medications. Paracetamol is recommended as a first line

pharmacological treatment in many International expert guidelines, with a role in the management of mild to moderate pain in patients with no current comorbidities.

- National Institute for Health and Care Excellence: Osteoarthritis: care and management.(NICE, 2014)
- European League Against Rheumatism: EULAR evidence based recommendations for the management of hip osteoarthritis.(Zhang et al, 2005)
- Osteoarthritis Research Society International: OARSI guidelines for the non-surgical management of knee osteoarthritis.(McAlindon et al, 2014)
- US Department of Veterans Affairs/Department of Defense: VA/DoD clinical practice guidelines: the non-surgical management of hip and knee osteoarthritis.(VA/DoD, 2014)
- American College of Rheumatology: Recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee.(Hochberg et al, 2012)

The recently released Royal Australian College of General Practitioners (RACGP) guideline for the management of hip and knee OA (RACGP, 2018) state that "*Although there is no recommendation either for or against paracetamol, it may be reasonable to trial paracetamol for a short period in some people with knee and/or hip OA, with monitoring of possible adverse effects, then discontinue use if not effective*". The neutrality of this recommendation, versus the previous first-line position of paracetamol, is based on a 2015 systematic review that reported that the reduction in OA pain seen with regular paracetamol versus placebo was too small to be of clinical relevance.(Machado, 2015) The guidelines are non-specific in terms of distinguishing MR from IR paracetamol.

However, patients experience pain relief likely as a result of a host of reasons, including the effect of the drug itself in combination with an element of placebo effect, lifestyle changes, and the natural fluctuating course of pain in OA. Recognising this, a more recently meta-analysis has pooled pool data from individual studies regarding commonly prescribed pharmacologic OA treatments without subtracting the influence of placebo effect to produce an estimate of pain reduction that more closely represents patients' experiences.(Stewart, 2018)

They found that paracetamol had a similar percentage relative change in overall pain relief as other types of analgesics, including topical NSAIDs, oral NSAIDs, COX-2 inhibitors and opioids. Taking into account the safety profiles of these medicines, the authors conclude that *paracetamol may be a more appropriate first-line oral analgesic than are other oral analgesics*, including NSAIDs, COX-2 inhibitors and opioids.

Importantly, the approach suggested by the RACGP guidelines that "*..., it might be reasonable to trial paracetamol for a short period ...*" has been documented in an N of 1 trial (Yelland et al, 2007) which concluded that MR paracetamol in *"N-of-1 trials may provide a rational and effective method to best choose drugs for individuals with osteoarthritis.* ***SR [sic MR] paracetamol is more useful than celecoxib for most patients of whom management is uncertain****"*.

Consistent with these views, the updated NICE guidelines (NICE 2017) continue to recommend paracetamol ahead of other oral treatments: "*Healthcare professionals should*

consider offering paracetamol for pain relief in addition to core treatments; regular dosing may be required. Paracetamol and/or topical NSAIDs should be considered ahead of oral NSAIDs, COX-2 inhibitors or opioids."

3.3 Clinical rationale for using MR paracetamol

The clinical rationale for using an MR paracetamol formulation is to provide a product with an 8-hour duration of action to facilitate adherence and improved outcomes. Australia's National Prescribing Service reports that poor adherence to dosing schedules, particularly when prescribed "as needed manner" may lead patients to perceive that their treatment is ineffective.(NPS, 2006) As a result, the possibility that patients require additional or alternative analgesia is increased.

The recommended maximum daily dose of paracetamol for effective pain relief is 4000 mg/day. For standard (IR) paracetamol, this equates to two 500 mg tablets every 4-6 hours (4 times daily). MR paracetamol formulations provide equivalent efficacy as IR paracetamol formulations, with the advantage of sustained analgesia over an 8-hour period to enable a reduction in daily dose frequency (three doses per day versus four doses per day for IR paracetamol products).

An Australian retrospective cohort longitudinal analysis has been conducted to compare usage patterns of 665 mg MR paracetamol tablets versus IR paracetamol in patients (n=74,115) with OA over a 2-year period (Ortiz et al, 2016). Significantly more patients switched from IR to 665 mg paracetamol tablets than switched from 665 mg paracetamol tablets to IR paracetamol (13.2% vs 3.1%, $p<0.001$). Long-term continuous use, defined as "no gap in continuous therapy at 24 months", was higher amongst patients prescribed 665 mg paracetamol tablets than those prescribed IR paracetamol (26.1% [95% CI 24.5-26.8%] vs 11.9% [95% CI 10-8-13.1%, $p<0.001$). Use of opioid combinations or stronger opioids was also higher ($p<0.001$) in those patients taking IR paracetamol, indicating that patients taking 665 mg paracetamol tablets were less likely to move up the analgesic pyramid. The explanation given by the authors is that patients experienced better analgesia with 665 mg paracetamol tablets dosed TID than from the IR paracetamol. They also suggested that tablet burden and dose frequency were a barrier to appropriate use in patients who are prescribed IR paracetamol.

In an Australian preference study evaluating the utility of 665 mg paracetamol tablets, 8 out of 10 OA patients reported that a TID regimen would be easier to adhere to than a four-times daily (QID) regimen if paracetamol was to be taken regularly. The same study also found that 665 mg paracetamol tablets provided better overall joint pain relief and resulted in higher levels of satisfaction versus IR paracetamol.(Benson et al, 2009)

Fluctuations between C_{max} and C_{min} levels are smaller with MR paracetamol ($p<0.001$): compared to the standard IR paracetamol, 665 mg paracetamol tablets have been shown to provide a lower mean C_{max}, and higher mean C_{min}. In addition, the mean plasma paracetamol concentration for 665 mg paracetamol tablets remained consistently above the estimated EC_{50} ($t>4$ mg/ml) for paracetamol throughout the evaluation period, indicating that this would be expected to maintain a therapeutic effect for up to 8 hours, allowing TID dosing.(Bacon et al, 2001)

Given that joint pain is frequently a chronic complaint requiring long-term analgesic use, simplifying treatment regimens, improving patient convenience, adherence and improving overall quality of life and better health outcomes are key objectives that shape the way such conditions are managed.

MR paracetamol, with its less frequent dosing regime offers many benefits over IR paracetamol for chronic pain management. Although not formally demonstrated in a clinical trial setting, the potential benefits of this may include improved sleep quality and improvements in the patients' ability to resume everyday activities, which can contribute to improving their overall quality of life. Longer acting agents also enable a reduced frequency of dosing; reducing the pill burden for patients who dislike having to take pills every 4–6 hours (Benson, 2009). This benefit is of particular relevance in patients who require analgesic dosing beyond a single dose, in either acute or chronic pain states. In these patients, reduced pill burden may lead to improved adherence with recommended dosing, which may improve analgesic relief, and thereby enhance better health outcomes (Ortiz et al, 2016).

3.4 Use of MR paracetamol in Australia

The TGA Rescheduling Application cites difficulty in accurately estimating the use of MR paracetamol in Australia and relies on an analysis of PBS data (2013-2017) to demonstrate a decline in use from 2016, attributed to the change in PBS restrictions at that time. According to this data, supply of MR paracetamol via PBS prescription peaked at approximately 6,000,000 prescriptions in 2016.

Nielsen Scan sales data show that during 2016 there were 10,881,663 units (packs of 96-100 tablets depending on the brand) of MR paracetamol sold and that in 2017 this had increased to 11,670,812. This equates to approximately 1,000,000 units sold per month, which provides a more accurate appraisal of the widespread use of MR paracetamol based on actual consumer purchase data. These data support that MR paracetamol is widely used in Australia. Most importantly, that wide use is done so in recognition of the principal differences between MR paracetamol and IR paracetamol that contribute to both MR paracetamol's perceived and proven benefit. These differences are outlined in Sections 3.1, 3.2, 3.3 above.

Australian Health Communication Network (HCN) data (collected between January 2004 and September 2007, when MR paracetamol was available via PBS script) showed that 68% of MR paracetamol was prescribed at the maximum dose (two tablets three times daily) compared to only 48% for standard paracetamol, suggesting that GPs may be more likely to prescribe MR paracetamol at the maximum recommended dose than they are standard paracetamol. Prescription at the maximum dose is consistent with use for time contingent dosing, lending support to the hypothesis that MR paracetamol is more likely to be used in this manner than standard paracetamol. Anecdotally, patients distinguish between standard and MR paracetamol. Many OA patients view standard paracetamol more as an "as needed" medication, whereas MR paracetamol is regarded as an ongoing treatment regimen specific for their OA pain. This perspective further contributes to

improved compliance and thus better outcomes in the management of mild to moderate OA pain.

As outlined in the TGA Rescheduling Application a search of the Chemist's Warehouse website advertises packets of MR paracetamol 96 caplets starting at $5.99. However, this needs to be contextualized against the price of IR paracetamol such as Panamax (Sanofi), with packs of 100 tablets starting at $0.69. This up to eight-fold price premium between MR and IR paracetamol in a self-select pharmacy environment has proven to be compelling based its positioning (8-hour duration of action and convenience of three-times daily dosing). Therefore it can be quite logically reasoned that users are drawn to selecting MR paracetamol based on its longer duration of action and its more convenient, less frequent dosing schedule.

Thus, for the overwhelming majority of users, a more restrictive scheduling is unlikely to add value, but may add a barrier to accessing this medication. This may lead them to revert to using IR paracetamol, which may lead to increased use of other analgesics as was demonstrated in an Australian study (Ortiz et al 2016).

4 Safety profile of MR paracetamol

4.1 Safety profile of MR paracetamol in therapeutic use

Paracetamol is generally well tolerated when taken at approved therapeutic doses of up to 4000 mg daily in divided doses in adults. The safety profile of MR paracetamol in normal therapeutic use is similar to that for IR paracetamol. Dart et al conducted a literature review to summarise the safety profile of MR paracetamol; based on data in 14 published clinical trials (therapeutic doses) they concluded that during therapeutic use, minor effects such as gastrointestinal upset and headache may occur; while the rate of these effects varies substantially among studies overall it is no different to that seen with IR paracetamol.(Dart et al, 2005)

4.2 MR paracetamol: Overdose cases originating from the literature

A comprehensive literature search was conducted by GSK that focused on toxicity associated with MR paracetamol formulations, irrespective of manufacturer. The following keywords were used for the search: 'paracetamol toxicity' and 'controlled release formulations'. A total of 53 articles were yielded, and were reviewed to determine those relating to overdose. The relevant articles are summarized below with key attention on clinical/ laboratory findings and outcome (mortality/morbidly) in overdose experiences.

Several case series, in which overdose with 665 mg MR paracetamol have been reported, are documented in the literature. The majority of cases of paracetamol MR overdose described in published literature show clinical/laboratory effects of increased liver enzymes, increases in prothrombin time, severe hepatotoxicity (alanine aminotransferase >1000 IU/L) or acute liver failure.

The treatments offered to patients who had ingested overdoses vary by country, according to local guidelines. The majority of these case reports (summarised below) originate from Australia (which is to be expected given that [redacted] annually originate in Australia); Notably, the established Australian and New Zealand overdose treatment protocols were sufficient to prevent any serious outcomes associated with MR paracetamol overdose.

- Dart et al 2005 [USA] published a review looking at the safety of paracetamol 650 mg MR both at the therapeutic dose and in overdose. In their review the authors described two fatal cases associated with ingestion of paracetamol MR reported in the Toxic Exposure Surveillance System database (TESS) between 1994 and 2002, however the exact cause of death was not confirmed in either case. During this time, there were a total of 3003 cases in which a paracetamol MR product was identified (Dart et al 2005).
- Roberts and Buckley 2008 [Australia] described the clinical course of a 25 year old female patient (B0500680A) who acutely ingested 96 (64g) tablets of 665 mg MR paracetamol. The patient presented at 14.5 hours post ingestion with a paracetamol concentration of 2235 µmol/L. Treatment was provided with anti-emetics and acetylcysteine, with blood sampling every 6 hours to guide treatment. The patient remained clinically well throughout her experience (Roberts et al 2008).
- Graudins et al 2009 [Australia] presented a report (B0591340A) from Australia, concerning a 72 year old female patient whom following acute ingestion (79 g) of 665 mg MR paracetamol presented with dual peaks in paracetamol serum concentration, and elevation in liver enzymes which resolved following treatment. The authors in this case postulated that the dual peaks resulted from the sequential release of drug firstly from the immediate release fraction of the tablet and then the modified-release fraction (Graudins et al 2009).
- Graudins et al 2010 [Australia] presented a case series of 4 patients who experienced acute intoxication, 2 (B0493857A, B0506468A) of whom had received 665 mg MR paracetamol tablets. In this case series, paracetamol concentrations showed an initial plateau absorption phase in the first 6–8 hours post ingestion and then remained persistently elevated above the paracetamol treatment nomogram line during the following 16–18 hours post ingestion. It was noted that both patients recovered following treatment (Graudins et al 2010).
- Graudins 2014 [Australia] conducted a retrospective review of 665 mg MR paracetamol poisonings occurring at the Monash Health Emergency Department, Australia between 1 October 2009 and 30 September 2013 to determine if the management of identified cases was consistent with existing guidelines. Graudins identified 42 cases of MR paracetamol overdose, of which 5 patients (B1008372A, B1008411A, B1008412A, B1008413A, B1008414A) developed non-serious alanine aminotransferase elevations which resolved following treatment. There were no patients with acute liver

failure and no fatalities were noted. From this retrospective review Graudins notes most patients presenting with MR paracetamol poisoning requiring acetylcysteine treatment had an initial serum paracetamol concentration indicating the need for treatment. The current Australian and New Zealand nomogram for paracetamol poisoning would have detected all cases requiring acetylcysteine treatment (Graudins 2014).

- Tellerup et al 2016 [Sweden] described a case (SE2016082274) of liver damage following an overdose of paracetamol, in a 48 year old male patient who ingested 66.5g of 665 mg MR paracetamol. One hour following ingestion, he presented to the hospital with an initial paracetamol concentration of 1032 mmol/L, with normal liver function tests, acetylcysteine was started immediately, 18 hours post admission paracetamol concentrations rose to 2871 mmol/L and a second course of acetylcysteine treatment was commenced. The patient developed liver damage with a peak alanine aminotransferase of 111 μkat/L (6660 U/L) at 113 hours (INR 2.0). The outcome for this patient was not reported (Tellerup et al 2016).
- Chiew et al, 2017a [Australia; The Australian Paracetamol Project] conducted a prospective observational study conducted with a focus on paracetamol MR overdose and associated liver injury and its treatment. Of 54 patients recruited within a study period of three years, 18 showed an increase in alanine aminotransferase > 50 U/L. Of these 18 patients, 10 patients further developed hepatotoxicity (alanine aminotransferase >1000 U/L). Chiew et al conclude that following acute overdose of MR paracetamol patients may have persistently high paracetamol concentrations for >24 hours. Paracetamol concentrations can be erratic with double or delayed paracetamol peaks. Later doses of acetylcysteine may need to be increased in patients with persistently high paracetamol concentrations. The median paracetamol dose was 31.9g. No fatalities were reported.
- Schultz et al, 2017 [Denmark] evaluated all enquiries received in the Danish Poison Information Centre (DPIC) involving ingestion of paracetamol MR. A total of 113 enquiries were received over a period of 10 years, including cases of suicidal attempts (n = 37) and medication errors (n=32). Of these 113 cases, 58 were classified in the two most severe classes of severity. Another 37 cases were classified into two classes with less severity or no risk of poisoning. The median paracetamol dose was 12g, no fatalities were reported (Schultz et al 2017).
- Salmonson et al, 2018 [Sweden] reviewed data from 145 medical records and included 53 cases in which acute ingestions of MR paracetamol greater than 10 g had been documented. The median reported dose was 20 g (range 10–166 166 g). None of the patients required a liver transplantation. However, Salmonson et al. report that:
    - Only 43 (81%) patients received acetylcysteine.
    - Acetylcysteine was commenced within 8 hours in only 34 (64%) patients.

- Eleven (21%) patients had serum alanine aminotransferase levels above the reference range at 24 hours:
  - Only 7 of these patients received acetylcysteine within 8 hours of ingestion and 3 developed liver toxicity.
  - A further 6 out of these 11 patients developed hepatotoxicity with alanine aminotransferase >1000 IU/L.

- Chiew et al, 2018 [Australia; Australian Toxicology Monitoring (ATOM)] conducted a prospective observational study to describe the clinical characteristics and outcomes of acute MR paracetamol overdoses. Patients were included if they had ingested a toxic dose (> 10 g) of MR paracetamol over a period of 8 hours or less. Of 116 patients recruited within a study period of 4.5 years, 113 (97%) were commenced on acetylcysteine. Serum paracetamol: 78 (67%) had a serum paracetamol level above the nomogram line at the initial measurement (≥ 4 hours), 6 patients had a double paracetamol peak of whom 3 were late line crossers and 2 developed hepatotoxicity. Outcomes: 21 (18%) patients developed hepatotoxicity, none required liver transplantation and none developed hepatic encephalopathy. The median paracetamol dose was 32 g, one fatality was reported but was not directly linked to the MR paracetamol ingestion (Chiew et al 2018).

The key finding from this literature is that the majority of patients recovered with or without treatment with acetylcysteine and none of the patients required a liver transplantation. **Overall, the review of published literature articles suggests that the nature, severity of the events, and outcome in overdose experiences with MR and IR formulations of paracetamol are not different.**

There has been only one death reported in Australia in association with paracetamol MR (an 87-year old man who died from respiratory failure secondary to aspiration 30 h post-ingestion of MR paracetamol) (Chiew et al 2018). There have been no deaths in patients who have developed hepatotoxicity subsequent to MR paracetamol overdose (Graudins 2014, Chiew et al 2018), and the number of toxic cases is proportionally lower compared to Sweden.

4.2.1 Analysis of MR paracetamol overdose cases in the GSK worldwide clinical safety database

To further understand the context of MR paracetamol overdose, a search of the GSK worldwide clinical safety database was undertaken on 07 July 2017 (prior to the withdrawal of the marketing authorisation in the EU):

[redacted]

[redacted]

A summary of the cases by source, age, gender, and country of origin (Table 3) demonstrates that the pattern of overdose associated with MR paracetamol is not different from IR paracetamol and share similar demographics of intentional overdose patients (female, teenage/young adults) (Schmidt 2005). There were two few cases of unintentional overdose on the GSK safety database to draw any conclusions.

Table 3. Overview of overdose cases associated with paracetamol 665 mg modified release tablets: Intentional versus Unintentional [redacted]

[redacted]

[redacted]

Data in the most recent annual report from the Uppsala Monitoring Centre (the WHO Collaborating Centre for International Drug Monitoring) establishes that the frequency of individual case safety reports per million inhabitants is similar in Australia, New Zealand and Sweden, suggesting that the country-specific disparities in MR paracetamol overdose figures are unlikely to be the result of a bias in reporting standards between these markets (Upsala, 2017).

This data arguably provides some insight on the action taken by Sweden to raise the matter with the PRAC. However, the situation in Australia is different; the proportion of

intentional overdoses is substantially smaller and there are no data suggesting unintentional or accidental overdose to be a significant issue in this market.

4.2.2 Local safety data

From the Submission:
"Data provided by the NSW PIC and the findings of the Australian Paracetamol Project study highlight the additional risks of hepatoxicity with MR paracetamol compared with IR paracetamol."

4.2.2.1 NSW Poisons Information Centre

The TGA Rescheduling Application states that paracetamol overdose is common and cites data from 2016 to show that there were 8,341 cases of paracetamol overdose (nature unspecified) reported to the NSW poisons information centres (PIC) and 818 (9.8%) of these involved MR paracetamol. Equating this data to the tablet sales of MR paracetamol in 2016 there were 0.698 (818/1,171,103,753) PIC inquiries per 1 million tablets sold.

The TGA Rescheduling Application notes that the number of calls relating to MR paracetamol is a small proportion of all paracetamol cases and acute overdoses with >10g (the toxic threshold for treatment) is uncommon. The TGA Rescheduling Application states that the overall number of cases of overdose related to MR paracetamol is increasing (TGA Rescheduling Application, page 18). However, data presented in the submission (Table 3, page 19) do not support this. In 2015 calls regarding intentional overdose with MR paracetamol were 13.73% (263/1915) of those with for all single active ingredient paracetamol formulations, whereas in 2016 the corresponding number is 12.7% (262/2052).

Equating this data to the tablet sales of MR paracetamol during these time periods further supports this:

- In 2015 there were 0.261 (263/1,007,978,112) cases of intentional toxic overdose per 1 million tablets sold.
- In 2016 there were 0.223 (262/1,171,103,753) cases of intentional toxic overdose per 1 million tablets sold.

Thus, although sales of MR did increase over the period analysed by the TGA, the number of extrapolated calls to all PICs remained unchanged, supporting the view that patient confusion is not increasing and does not warrant the proposed rescheduling.

4.2.2.2 *Australian Paracetamol Project*

This paper provides an analysis of outcomes following acute overdoses with MR paracetamol in the Australian setting. The median dose ingested was 32g (range: 20-49g). The number of patients who developed hepatoxicity, despite early treatment, were low.

Larger ingested dose (in 0.1 g/kg increments), higher paracetamol ratio and longer time to acetylcysteine were all associated with a significant increased risk of hepatotoxicity.

The data observed in this paper raise questions about the optimum treatment of large (≥40 g) overdoses with MR paracetamol.(Chiew et al, 2018) Whilst the mean dose taken in this cohort was below this level, it is cited as a hypothetical concern because of the pack size available.

On the basis of their research, Chiew et al, recommend that patients with large (≥ 40 g) acute overdoses of MR paracetamol have repeat paracetamol concentrations to guide increased and prolonged administration of acetylcysteine and/or repeated doses of activated charcoal (Chiew et al 2018). The results from a PK modelling study, undertaken by GSKCH (GSKCH, 2017), corroborate this, and indicate that further additions to optimise the existing protocol for treatment of overdose with MR paracetamol may be warranted.

GSKCH is actively supporting the communication of a new edition of the local paracetamol overdose guidelines, which are in preparation for publication in the near term.

4.2.3 Analysis of MR paracetamol reports in the Database of Adverse Event Notifications when compared to a similarly scheduled analgesic used in the treatment of OA pain

4.2.3.1 Position of ibuprofen elevated in OA guidelines

The recently released Royal Australian College of General Practitioners (RACGP) guideline for the management of hip and knee OA (RACGP, 2018) suggest that, *"Nonsteroidal anti-inflammatory drugs (NSAIDs; eg ibuprofen), taken orally at low doses for short periods are recommended for some people with knee and/or hip OA. Monitoring for possible adverse effects of the drugs is necessary."*

It can reasonably be expected that healthcare professionals will look to apply such a recommendation and that medicines sponsors will promote OTC NSAIDs based on this RACGP recommendation. As a case in point, Ibuprofen is a widely available NSAID and is presently indicated and promoted for the treatment of OA pain based on the RACGP guidelines.

4.2.3.2 TGA/ACMS review of ibuprofen scheduling

Ibuprofen was also selected as a valid comparator in this instance because it has recently (November 2017) undergone a scheduling review by the ACMS resulting from a request that it be rescheduled to higher schedules in the SUSMP in much the same way as this

current proposal for MR paracetamol.[§] The grounds for the request were in response to recent and mounting evidence regarding the risks associated with NSAIDs and the related concern that larger packs of ibuprofen for longer term use should only be available as a Schedule 3 medicine to ensure mandatory intervention of a pharmacist to determine whether a larger pack size is therapeutically appropriate.

The TGA Database of Adverse Event Notifications (DAEN) contains information from reports of adverse events that the TGA has received in relation to medicines in Australia. As part of its considerations, the delegate's interim decision on ibuprofen draws on data from the DAEN. While a key consideration in relation to the toxicity of ibuprofen was that it "*has a wide therapeutic window and when taken orally, the propensity for toxicity in overdose is low*." The DAEN data noted 35 cases where death was a reported outcome in relation to this medicine.

Ibuprofen is regarded as being generally benign in overdose. The majority of patients with acute ibuprofen overdose will remain asymptomatic or develop minor self-limiting gastrointestinal symptoms. However, serious clinical sequelae have been reported in patients with acute ibuprofen overdose and these include convulsions, metabolic acidosis, coma and acute renal failure.(Hunter, 2011) The management of these serious clinical features is supportive and there are no specific antidotes for acute ibuprofen toxicity.

There are no established guidelines for ibuprofen overdose management in Australia. This is highly relevant given that the impetus behind the MR paracetamol scheduling submission is the purported inadequacy of the Australian paracetamol overdose guidelines for the management of overdose with MR paracetamol.

Submissions in support of the TGA/ACMS proposal to reschedule ibuprofen cited concerns that the recent rescheduling of codeine is likely to increase the use of ibuprofen. Advertising in relation to the newly released RACGP OA management guidelines further elevate this concern. Despite this, the delegate's interim decision was that the current scheduling of 200mg ibuprofen tablets (2 x 200mg TID – i.e. 1200mg/day) remains appropriately scheduled (Schedule 2/Exempt). The delegate's final decision confirmed the interim decision.

4.2.3.3 DAEN data: MR paracetamol versus ibuprofen

Ibuprofen at a dose of 2 x 200mg TID (1200mg/day) is scheduled in the SUSMP as a Schedule 2 (Pharmacy Medicine) in pack sizes up to 100 tablets (and is exempt from scheduling in pack sizes of less than 25 tablets). Hence, for the purposes of comparison, it has similar scheduling, dosing frequency and availability to MR paracetamol.

For the purposes of comparison, GSK has conducted an analysis of the DAEN database for the period 01 June 2001 - 17 Feb 2018 in order to equate reports of adverse events

[§] Source: http://www.tga.gov.au/book-page/16-ibuprofen

[redacted]

with MR paracetamol and to compare these data with those of ibuprofen 200mg tablets, (Table 4). The search was limited to reports within the Medical Dictionary for Regulatory Activities (MedDRA) system organ class "*Injury, poisoning and procedural complications*", being relevant to the question at hand.

Table 4. Summary of DAEN case data for MR paracetamol and Ibuprofen

	MR paracetamol*		Ibuprofen*	
	All cases	**Overdose**	All cases	**Overdose**
Number of reports (cases)	49	**40**	74	**24**
Number of cases with a single suspected medicine	32	**27**	36	**10**
Number of cases where death was a reported outcome	2	**0**	15	**3**

* Medicines included in the DAEN search:

MR Paracetamol: Duatrol SR (Paracetamol), Osteomol 665 Paracetamol (Paracetamol), Panadol Extend (Paracetamol), Panadol Osteo (Paracetamol).

Ibuprofen 200mg tablets: Act-3 (Ibuprofen), Actiprofen (Ibuprofen), Advil (Ibuprofen), APOHEALTH Ibuprofen (Ibuprofen), Chemists' Own Ibuprofen (Ibuprofen), Coles Ibuprofen (Ibuprofen), Hedafen (Ibuprofen), Hedafen Ibuprofen (Ibuprofen), Herron Ibuprofen (Ibuprofen), Herron Ibuprofen Blue (Ibuprofen), Home Brand Ibuprofen (Ibuprofen), Niapren (Ibuprofen), Not specified (Ibuprofen), Nurofen (Ibuprofen), Nurofen Zavance (Ibuprofen), Panafen IB (Ibuprofen), Pedea (Ibuprofen Lysine), Pharmacy Choice Ibuprofen (Ibuprofen), Rafen (Ibuprofen), Terry White Chemists Ibuprofen (Ibuprofen), Tri-profen (Ibuprofen), You'll Love Coles Ibuprofen (Ibuprofen)

Review of the DAEN data is limited by the small number of cases for both medicine. However, it indicates that there are more "*Injury, poisoning and procedural complications"* case reports overall with ibuprofen (74 vs 49), more cases with a single suspected medicine (36 vs 32) and 7-fold more cases of death (15 vs 2) than with MR paracetamol. For both medicines, overdose was the most frequently cited MedDRA reaction term. The frequency of overdose cases in which was higher with MR paracetamol than with ibuprofen (40 vs 24). However, there were no deaths – 0% (0/40 overdose cases) with MR paracetamol, whereas with ibuprofen there were three deaths – this equates to 1 in 8 (12.5%; 3/24 overdose cases) of the overdoses cases reported resulting in death.

The delegate's interim decision (and final decision) was to retain the current scheduling of 200mg ibuprofen tablets. The DAEN analysis above shows MR paracetamol to have a similar, if not better, safety profile in overdose than does ibuprofen. Restricting access to MR paracetamol presents consumers with an unnecessary barrier to access this product, despite data supporting it to be as safe in use as ibuprofen.

[redacted]

Importantly, IR paracetamol alone cannot fill the void that will be created by the proposed rescheduling, as evidenced by the clear and evidenced preference of consumers who are drawn to MR paracetamol based on its longer duration of action and its more convenient, less frequent dosing schedule.

For most users, a more restrictive scheduling is unlikely to add value, but may also add barriers to accessing this medication, such as increased cost to consumers and time spent at point of purchase.

5 MR paracetamol: risk:benefit profile in OA

For the purposes benefit/risk analysis, the Brass methodology for the benefit risk assessment of non-prescription drugs has been used.(Brass et al, 2011; Brass et al, 2013)

Each of the possible benefit and risk attributes of an MR paracetamol formulation has been consolidated using a value-tree framework (Figure 1). MR paracetamol formulations provide a longer-lasting analgesic effect than do IR paracetamol formulations. The potential benefits are that this may help prevent sleep interruptions due to pain and may help to improve patients' ability to resume everyday activities, which could contribute to improving a pain sufferers' overall quality of life. This benefit is of particular relevance in patients who require analgesic dosing beyond a single dose, in either acute or chronic pain states.

The plausibility of these potential risk and benefit attributes has then been ascertained based on available data (citations listed), identified data gaps (listed as UNK) or non-applicability (N/A), as shown in Table 5.

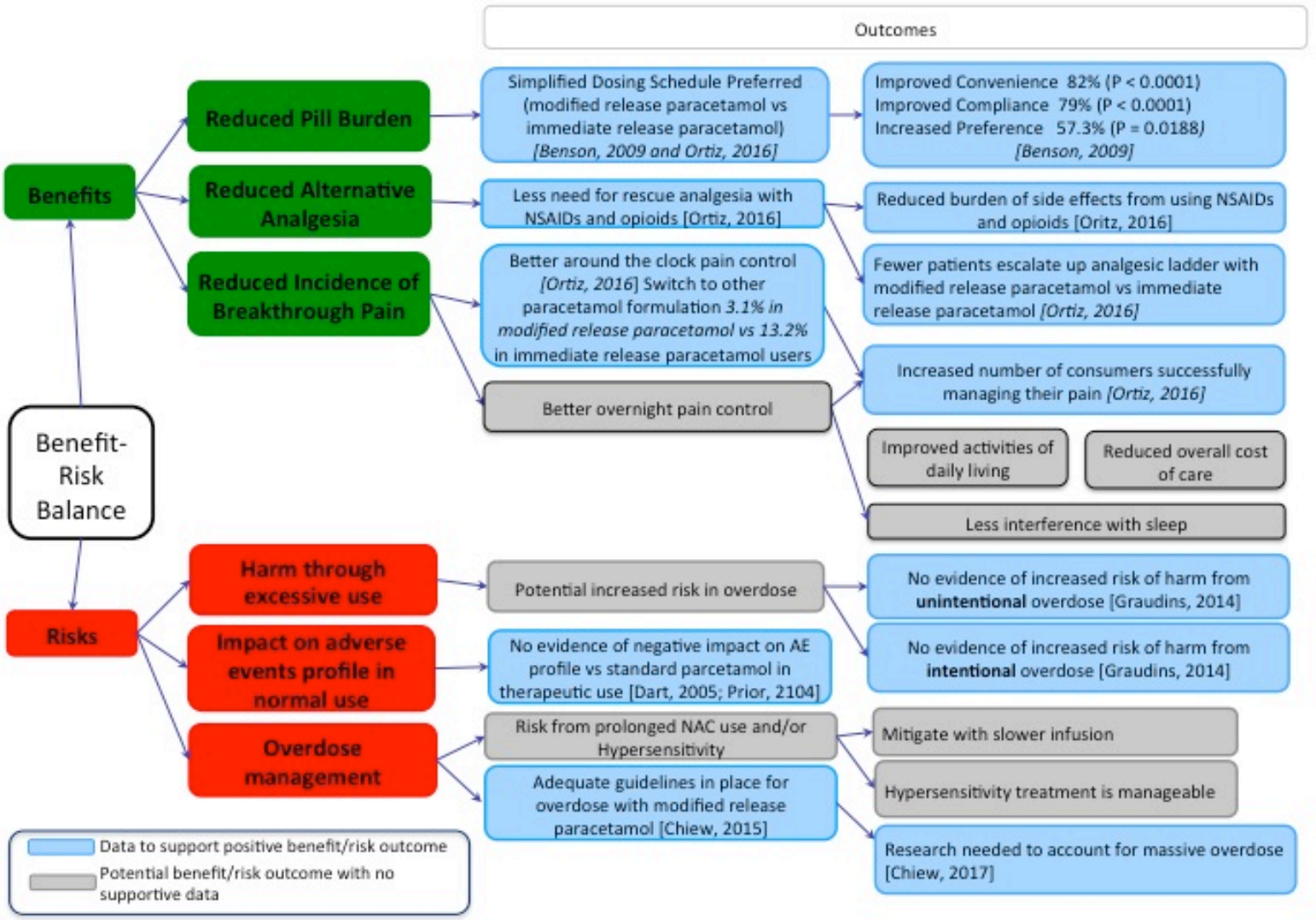
Table 5. Data supporting potential benefit and risk attributes of using an MR paracetamol formulation instead on an IR formulation in the current Australian context

BENEFIT ATTRIBUTES [✓ indicates that available data supports these benefits and outcomes]	
Feature: Three times daily dosing	
Reduced pill burden	✓ **(Ortiz, 2016; Benson, 2009)**
Simplified dosing schedule	✓ **(Ortiz, 2016; Benson, 2009)**
Improved convenience	✓ **(Ortiz, 2016; Benson, 2009)**
Increased user preference	✓ **(Ortiz, 2016; Benson, 2009)**
Improved compliance	✓ **(Ortiz, 2016;)**
Feature: Steady state serum concentration	
Better around-the-clock pain control	✓ **(Ortiz, 2016; Bacon, 2002)**
Better overnight pain control	**UNK**
Reduced incidence of breakthrough pain	✓ **(Ortiz, 2016; Bacon, 2002)**
Outcome: Rescue/Alternative analgesia	
Less need to escalate to narcotic analgesics	✓ **(Ortiz, 2016)**
Reduced burden of side effects from using opioids	✓ **(Ortiz, 2016)**
Reduced burden of side effects from using NSAIDs	**UNK**
Outcome: Impact on quality of life	

[redacted]

Increased number of consumers successfully managing their pain	✓ **(Ortiz, 2016)**
Improved activities of daily living	**UNK**
Improved sleep quality	**UNK**
Reduced overall cost of care	**UNK**
RISK ATTRIBUTES [× indicates that these risk concerns are not supported (negated by) the available data]	
Concern: Harm through excessive use	
Increased adverse events due to exceeding dose and/or duration of use vs IR	**UNK**
Increased potential for risk from unintentional overdose vs IR	× **(Graudins, 2014)**
Increased risk of hepatotoxicity in overdose vs IR	× **(Dart, 2005; Graudins, 2014)**
Increased potential for risk from intentional overdose vs IR	× **(Graudins, 2014)**
Concern: Impact on adverse event profile	
Increase risk of adverse events in normal use due to higher apap dose vs IR	× **(Dart, 2005; Prior, 2014)**
Concern: Overdose management	
Further research needed in massive overdose	✓ (Chiew et al, 2017)
Adequacy of current local management practices	✓ (Chiew et al, 2015)
Potential for risk from extended exposure to NAC	**UNK**

Figure 1. Value-Tree Framework – benefit and risk attributes of MR paracetamol formulation versus IR paracetamol formulation in chronic pain states in the current Australian context



[redacted]

6 Management of MR paracetamol overdose

6.1.1.1 Analysis of the management of MR paracetamol overdose cases in which hepatic toxicity has been reported

[redacted]

A review of the post-marketing data confirmed that delayed peaks of serum paracetamol drug levels could occur following overdose with MR paracetamol. Treating physicians

should utilize existing paracetamol overdose management protocols as a guide. However due to delay in peak paracetamol levels multiple serum samples should be taken to guide appropriate management. If any liver injury is suspected treatment with NAC should continue accordingly, or, if elevated levels of paracetamol continue, treatment with NAC should be maintained as clinically indicated, until confirmation that peaked levels are declining and the patient is no longer at risk of on-going hepatic injury. The benefits of prolonged NAC treatment outweigh any incremental risk.

The Australian and New Zealand paracetamol overdose guidelines combine an upper threshold (>10 g paracetamol) for the treatment of overdose with a single nomogram line for people with a suspected overdose below this toxic threshold. The above findings confirm that they mitigate risk of hepatoxicity from MR paracetamol overdose, as they do for IR paracetamol.

This position is further strengthened with the data from a [redacted] and prior analysis showing that almost twice as many cases are appropriately managed when using an upper threshold for treatment of overdose (as used in Australia) rather than timed serum paracetamol concentration on a more conservative nomogram line (as used in Sweden) [96.4% vs 57.8%, see also section 10.1.5].

7 MR paracetamol overdose in different markets

7.1 Key differences in the misuse of paracetamol in Sweden contribute to its safety in use in Australia

The situation in Sweden is different to that in other markets, including Australia. Prior to their removal from the market, the classification, marketing and funding of MR paracetamol products in Sweden had meant that their availability for use as agents for overdose was considerably higher in Sweden than is currently the case in Australia, despite its Schedule 2 availability.

The majority of cases of overdose with MR paracetamol are intentional (Table 3, Section 4.2.1). Key differences between the MR paracetamol products in Australia and Sweden are summarised in Table 6. This information clearly shows that there is a different pattern of misuse of MR paracetamol in Sweden leading to a higher burden of overdose than there is in Australia, despite the product being available self-select to consumers inside Pharmacies in Australia. A similar favourable situation to that of Australia exists in New Zealand.

[redacted]

Table 6. Contributors to the differences in availability of MR paracetamol as a potential agent to be used in overdose: Sweden versus Australia (and New Zealand)

	Australia	New Zealand	Sweden
Medicine Scheduling (tion)	Schedule 2	Schedule 2	Schedule 4 (Prescription)
Cost of supply	Consumer pays	Consumer pays	Funded prescription medicines are free of charge to the consumer once they have met the annual threshold for out-of-pocket expenditure on prescription items*
Labelled indications	Persistent pain associated with osteoarthritis.	Persistent pain associated with osteoarthritis.	Acute and chronic pain states, including headache, period pain, toothache, symptoms associated with cold and flu, fever, muscle and joint pain, pain associated with osteoarthritis
Total paracetamol calls to PIC	8341 (in 2016)†	13,594 over 10 years*	4391 (in 2016)*
MR paracetamol calls as a percentage of total paracetamol calls to poisons centres	9.8% (818/8341) †	0.22% (31/13954)*	22%*

* Data sourced from NZ MARC review report – 7 December 2017;
† Data sourced from TGA Scheduling Application page 18.

7.1.1 Despite different medicines scheduling (classification) the incidence of overdose with MR paracetamol is very low in Australia

Available local evidence supports the positive benefit-risk profile of MR paracetamol when used as indicated in Australia.

Given that management of overdose with MR paracetamol was the primary impetus behind the EMA PRAC review, it is of value to compare the incidence of overdose in Australia versus that in Europe. To achieve this, the number of calls to Poisons Information Centres has been correlated with the sales data to obtain a common measure

[redacted]

of the number of calls per 1 million modified-release paracetamol tablets sold. Available data for Australia, Sweden, Denmark and New Zealand for the year 2016-2017 are summarised below (Table 7). Where the number of calls are stated they refer to all possible cases (i.e. intentional, unintentional and accidental exposures).

Table 7. By-country comparison of the rates of PIC calls per million MR tablets sold

	Australia	**Sweden**	**Denmark**	**New Zealand**
Year	2016	2016	2016-17	2016-17
Medicine Scheduling (Classification)	Pharmacy Medicine	Prescription	Prescription	Pharmacy Medicine
Number of calls to PIC				
Paracetamol	8341	4391	-	1600*
Modified-release paracetamol	818	922	123	13
Proportion of paracetamol calls relating to modified-release paracetamol	**9.8%**	**22%**	**-**	**0.4%**
Number of tablets sold	1,171,103,753	255,138,461	148,258,200	14,395,363
PIC inquires per 1 million tablets sold	**0.698**	**3.614**	**0.830**	**0.903**

PIC = Poisons Information centre.

* Calculated average based on all paracetamol calls made to New Zealand Poisons Information Centre between 1 Jan 2008 and 10 August 2016.

Data sources: Calls volume data for modified-release paracetamol sourced from MARC review report – 7 December 2017, correspondence with New Zealand PIC, and correspondence with Danish Giftlinjen. Sales data sourced from IMS data (sales to Pharmacy) for Sweden and Denmark and AC Nielsen data for Australia and New Zealand.

The above data demonstrates significant differences in the number of call and proportion of calls relating to modified-release paracetamol in these three markets. In Sweden there were 922 calls (22% of all paracetamol calls) in a year, whilst in Australia there are a similar number, this is a much lower proportion compared to total paracetamol calls (9.8% of all paracetamol calls).

This data shows that in 2016 in Australia there was an average of **0.698 inquiries per 1 million modified-release paracetamol tablets sold.** This is lower than that observed in all other countries analysed, despite sales being significantly higher in Australia than in other markets. The data shows that the there is a more than 5-fold higher incidence of inquires relating to MR paracetamol in Sweden than in Australia, despite higher sales and less restrictive access in Australia. Both Denmark and New Zealand also display a significant difference to Sweden, where there was a 4-fold higher incidence of **3.614 inquiries per 1 million modified-release paracetamol tablets sold** compared to either of these two countries.

[redacted]

Accessibility to means is considered to be a risk factor for self-harm. However, the data from Australia, Denmark and New Zealand provide compelling evidence that in countries where best practice overdose guidelines are established differences in medicines scheduling status did not appear to have had impact on the incidence of overdose. This negates the proposition that rescheduling may pre-emptively prevent higher incidence rates that have been observed elsewhere. Further it provides support to retain the current scheduling given that there is an extremely low incidence of incidence of overdose events relating to the consumption of MR paracetamol given the large number of dosage units that are sold in Australia. Restricting availability, and providing additional healthcare professional intervention, will not provide any significant additional benefit to this safety profile.

- **Unlike in Sweden, high incidence rates of overdose with MR paracetamol have not been observed in Australia, New Zealand or in Denmark.**
- **Despite MR paracetamol being available only on prescription in Sweden the rates of inquiries to the Poisons Information Centre were 5-fold higher than in Australia.**
- **The different medicines scheduling statuses in these markets do not appear to have impacted the incidence rates of overdose.**

8 MR paracetamol availability in other markets

8.1 The Danish Medicines Agency has annulled the modified-release paracetamol marketing suspension

As is the case in Australia, Denmark also has its own paracetamol overdose treatment protocol, which was established in 2013 (Andersen, 2013). Having presented the details of this protocol to their local health authority, the protocol was found to be sufficient to enable an over-ruling of the PRAC recommendation. Consequently, on 16 May 2018, the **Danish Medicines Agency** announced an annulment of the European Commission marketing suspension on modified-release paracetamol. Modified-release paracetamol therefore remains on the market (Danish Medicines Agency, 2018).

The grounds for the decision to continue to allow the sale of modified-release paracetamol in Denmark were as follows:

- The Danish paracetamol overdose treatment protocol (Andersen, 2013) is different to that used in Sweden. Like the protocol in Australia, the **Danish protocol is also based on a paracetamol dose approach.** All patients are treated on suspicion of poisoning without waiting for a response from blood tests and the duration of antidote treatment is adjusted to the individual patient.
- Data from the "Giftlinjen" (the Danish Poisons Information Centre) do not demonstrate significant safety signaling related to overdose with modified-release paracetamol products in this market. This data shows 55 inquiries regarding modified-release

paracetamol in 2016 and 68 in 2017; these numbers equate to an essentially unchanged trend of 0.83 inquiries per 1 million modified-release paracetamol tablets sold[**] over the period.

8.2 Situation in New Zealand

At its 60th meeting (26 April 2018), the Medicines Classification Committee (MCC) discussed a proposal to reclassify MR paracetamol from pharmacy-only medicine to restricted medicine. In the MCC 60th meeting minutes (published 15 June 2018) it was recommended that this proposal be upheld. Per the MCC processes, GSKCH submitted an objection to this recommendation in which three separate reasons as grounds for objection were presented:

- Practical differences between the paracetamol overdose guidelines in different countries
- Current situation in Europe (Denmark)
- Newly approved, re-designed packaging enhances product differentiation

Medsafe accepted the objection as valid on the basis that new information has been available and that the MCC did not consider all the safety and benefit issues correctly. This will be reconsidered at the MCC 61st meeting as agenda item 5.1.1 - Reclassification of modified release paracetamol – objection to the proposed recommendation that modified release paracetamol be reclassified from a pharmacy-only medicine to a restricted medicine.

8.3 Situation in other European countries

The process to lift the marketing suspension on modified-release paracetamol is currently on-going in several other European countries, including Finland (where a submission requesting a lifting of the suspension has been filed with the regulator) and Belgium.

Key elements of this process include utilisation of the EMA PRAC overdose guidance (as discussed above) and the introduction of additional risk mitigation strategies such as suitable paracetamol overdose guidelines, blister packaging and consumer education. All of these risk mitigation strategies have been in place in Australia for over 17 years.

[**] Data source: Calls volume data for modified-release paracetamol sourced from correspondence with Danish Poisons Information Centre (Giftlinjen) and sales data sourced from IMS data (sales to Pharmacy).

[redacted]

9 Implications of the pharmacokinetics of MR paracetamol on overdose

From the Submission:
"The complex and unpredictable pharmacokinetic profile of MR paracetamol following an overdose means that the continued availability of MR paracetamol in pack sizes of 96 caplets as a schedule 2 medicine poses an unacceptable to risk to the Australian population."

9.1 Modeling and simulation analysis of paracetamol concentrations in the overdose setting

A population pharmacokinetic model has been developed [redacted]

Findings from these investigations suggest that initiating treatment with antidote as soon as possible after ingestion of a potential overdose is important in mitigating the toxicity of paracetamol overdose. It also suggests than in the past, it has been possible to miss or delay treatment due to low concentrations within the designated sampling window subsequently elevating. The modeling suggests that on a pharmacokinetic basis, the first dose level at which one can expect concentrations above the nomogram level is a 10 g acute ingestion; however, this is expected to occur outside of the designated 4 – 8 hour sampling time window. These points highlight the importance of establishing a minimum dose threshold above which treatment should be started immediately. This can also be applied to situations where time of ingestion, dose, or formulation are not known.

Based on an analysis of the pharmacovigilance data, the paradigms for management of paracetamol overdose in Denmark, Sweden, and Australia/New Zealand are efficient for identifying and treating the great majority of cases. However, the results from this PK modelling study indicate that further additions to optimise the existing protocol for treatment of overdose with MR paracetamol may be warranted.

- Multiple sampling – GSKCH recommends that blood samples to measure serum paracetamol levels should be taken 4, 6 and 8 hours after ingestion (not 4 and 8 as in the existing Australian and New Zealand guidelines). GSKCH is discussing the utility of calculating paracetamol half-lives in the management of overdose with Poisons Information Centres as this is not a routine part of current clinical practice. The use of half-lives represents a novel approach for the management of paracetamol overdose, which allows for earlier detection for the need for treatment with antidote, which may further improve the outcomes of patients in an overdose setting.
- Time period for monitoring – Due to elevated serum paracetamol concentrations extending for up to 48 h, GSKCH recommends that patients who have ingested

MR paracetamol should be adequately monitored. Moreover, where dose, time of ingestion, or formulation is not known, patients should be treated with antidote immediately while continuing to monitor paracetamol concentrations and signs of hepatic injury. Monitoring and treatment with acetylcysteine should continue until serum paracetamol levels and liver functions have normalised.

These results are corroborated independently by the recommendation of Chiew et al, that patients with large (≥ 40 g) acute overdoses of MR paracetamol have repeat paracetamol concentrations to guide increased and prolonged administration of acetylcysteine and/or repeated doses of activated charcoal (Chiew et al 2018).

Current data from [redacted] and from the Chiew et al 2018 analysis, alongside the very low reported incidence of overdose cases and an absence of fatalities with MR paracetamol in New Zealand, do not suggest an inadequacy of the current Australian and New Zealand guidelines. Rather they underscore opportunities to further refine the protocols for managing overdose with MR paracetamol.

10 Adequacy of Australian overdose management guidelines

10.1 Local overdose guidelines

Established Australian and New Zealand paracetamol overdose guidelines contain specific and explicit instructions on how to manage overdose with MR paracetamol (Chiew et al 2015). These instructions take into account the bi-phasic and prolonged pattern of paracetamol absorption from MR formulations and are distinct from the standard treatment protocol. After very large overdoses, the IR paracetamol formulation demonstrates the same pharmacokinetic profile ([redacted]).

The original paracetamol overdose management guidelines for use in the local market, published in March 1997, were prepared by an Australasian Working Group in consultation with a number of University Hospital groups involved in the clinical management of paracetamol overdose in Australia and New Zealand, and with the Australasian College for Emergency Medicine. The guidelines comprised an explanatory booklet and a wall-chart poster. GSKCH funded this initial program and has maintained updates of the guidelines over several years. The original guidelines were for use in management of overdose with preparations containing IR paracetamol.

In 2001, prior to the Australian launch of 665 mg MR paracetamol, a major revision of the guidelines was undertaken in order to incorporate information about the management of overdose with MR paracetamol formulations. These amendments were based on data extracted from a GSKCH Expert Report on the clinical documentation of MR paracetamol as well as review and comment from Professor Peter Carroll (Pharmacologist) and Dr John Vinen (Emergency Medicine Specialist), both of whom were involved in the development of the original guidelines. Further minor revisions were made in 2002.

[redacted]

In 2005, further amendments were made based on data from an Australian study on the comparative pharmacokinetics of IR and MR paracetamol in a volunteer model of simulated overdose (Tan et al 2006). Dr Andis Graudins (Division of Clinical and Experimental Toxicology, Prince of Wales Hospital, Randwick, NSW, Australia) provided additional expert commentary regarding the appropriate course of action to take in the possibility of overdose with MR paracetamol.

Subsequently, GSKCH convened a meeting in June 2006 to reconcile updated overdose management advice for both IR and MR paracetamol formulations with current Australasian clinical toxicology practice. Revised consensus guidelines were developed by a panel of clinical toxicologists consulting to the Poisons Information Centres in Australia and New Zealand. The draft guidelines were presented for comment at a peer-review clinical toxicology meeting attended by clinical toxicologists from around Australia and New Zealand in January 2007. In 2008, these revised guidelines were published in the *Medical Journal of Australia* (Daly et al 2008).

A feature of the revised guideline was the adoption of a nomogram with a single line. This nomogram line, the Rumack-Matthew nomogram, was initially developed for use with IR paracetamol overdose in the US. The efficacy and safety of acetylcysteine dosing given according to this nomogram has been extensively reviewed and it has been demonstrated to be the treatment threshold which has the most clinical data to support its efficacy and safety (Smilkstein et al 1988). The adoption of the Rumack-Mathew nomogram in the Australian New Zealand guidelines was based on a desire to simplify decision-making; it lowered the previous Australian/New Zealand nomogram line by 25% so that it reduced the risk for misinterpretation and error. This provides both a margin of safety for patients who may possess risk factors and a small margin of error for estimation of time of ingestion, and avoids the need for potentially confusing additional lines (Daly et al 2008). The Swedish guidelines have two lines, the lower of which is used for patients presenting the MR paracetamol overdose. This is a fundamental difference compared with the local paracetamol overdose guidelines. However, the Australian and New Zealand toxicology experts agreed that having two lines was confusing, hence the reason for having only the one in the local guidelines. The revised guidelines further updated advice on the management of staggered paracetamol overdose and on overdose with MR paracetamol.

Most recently, the guidelines were further updated, independently of GSKCH, using a similar process to that described above. These updated guidelines were published in the *Medical Journal of Australia* in 2015 (Chiew et al 2015). The key changes from the previous guidelines released in 2008 are recommendations for management of liquid paracetamol ingestion in children, management of patients with large/massive overdoses, duration of acetylcysteine treatment in MR paracetamol ingestions, repeated supratherapeutic ingestions and indications for activated charcoal.

The Australian paracetamol overdose guidelines are under revision [redacted] s with previous iterations GSKCH has indicated a preparedness to support the communication of the new guidelines to the accident & emergency and toxicology community [redacted] for ease of access.

[redacted]

10.1.1 Current Australian overdose protocol

Within the current Australia and New Zealand Paracetamol overdose guidelines, the guidance for overdose with MR paracetamol is as follows (Chiew et al 2015):

- If more than 10 g or 200 mg/kg (whichever is less) has been ingested, **commence acetylcysteine**.
- Measure serum paracetamol concentration at 4 or more hours post-ingestion, then again 4 hours later if the first concentration is below the nomogram line.
- If serial paracetamol concentrations taken 4 hours apart are below the nomogram line **and decreasing**, acetylcysteine may be discontinued, otherwise continue the full 21-hour course of acetylcysteine to its completion.
- If < 10 g and < 200 mg/kg has been ingested, measure serum paracetamol levels to determine the need for acetylcysteine. Serum paracetamol concentrations should be taken at 4 hours or more post-ingestion (as with IR paracetamol preparations) and repeated 4 hours later. If either concentration is above the nomogram intervention line, acetylcysteine should be commenced.
- Near the planned completion of acetylcysteine infusion, a repeat ALT and paracetamol concentration should be measured. Treatment with acetylcysteine should be continued if the ALT is increasing (> 50 U/L) or the paracetamol concentration is greater than 10 mg/L (66 μmol/L). Acetylcysteine can be continued at a rate of 100 mg/kg of acetylcysteine in 1000 mL of 5% dextrose over 16 hours.

10.2 Overdose guidelines for MR paracetamol in Sweden

The Swedish guidelines for the management of paracetamol poisoning in Sweden were revised in 2016 to include advice on managing overdose with MR paracetamol following discussion of the Swedish case data (Hojer et al 2016), and adopted formally in January 2017.

Single toxic dose amounts in adults and children are 140 and 175 mg/kg, respectively. Blood sampling for serum paracetamol measurement is recommended 4 h post ingestion. Urgent blood sampling is recommended for those patients presenting >4 h post ingestion. **Blood sampling is recommended before initiation of treatment with acetylcysteine.** The rationale cited by these guidelines is the potential for acetylcysteine to cause false low values for serum paracetamol.

In MR paracetamol overdose, blood sampling is recommended at 4, 6, 12 and 18 h (even though acetylcysteine treatment may be in progress for the later time points) post paracetamol ingestion. A high (not defined) serum paracetamol concentration late (not defined) in the time course of sampling is justification for a dose increase in acetylcysteine. Rising serum paracetamol concentrations but falling below the nomogram treatment line are a justification for more frequent blood sampling.

[redacted]

Threshold values for serum paracetamol indicating that acetylcysteine treatment should be commenced in paracetamol overdose are lower for MR paracetamol overdose than for IR paracetamol overdose at all time points, creating a nomogram with two threshold lines. There is no difference between the initial acetylcysteine bolus dose between MR and IR paracetamol overdose protocols. The maintenance therapy for the MR paracetamol overdose patient is acetylcysteine at 12.5 mg/kg for 20 h, with a stop rule that serum paracetamol is undetectable.

10.2.1 Limitations of the Salmonson data set

A key limitation of the Swedish protocol is that it relies on the intoxicated patient to relate the time of ingested dose and acetylcysteine treatment can be delayed until serum-paracetamol levels are known. The conclusions from the Salmonson dataset, published online 23 June 2017 (Salmonson et al 2018), which evaluated outcomes based on an older Swedish protocol with no specific guidelines for MR paracetamol, highlight the inadequacy of using an overdose protocol designed for use with IR paracetamol in response to an overdose with an MR paracetamol product.

The Salmonson dataset reviewed data from 145 medical records and included 53 cases in which acute ingestions of MR paracetamol greater than 10 g had been documented (Salmonson et al 2018). The median reported dose was 20 g (range 10–166 166 g). None of the patients required a liver transplantation. No fatalities were reported.

Had the Australian and New Zealand guidelines been applied to these cases, treatment with acetylcysteine would have been initiated in **all 53 of these cases** at the time of admission. However, Salmonson et al. report that only 43 (81%) patients received acetylcysteine.

10.2.2 Comparison of overdose guidelines for MR paracetamol

The antidote, acetylcysteine, is effective if initiated early (within 8 h after an acute ingestion); its use minimises morbidity from paracetamol overdose (Daly et al 2008). One of the main concerns with managing overdose after MR paracetamol formulations is the issue of late nomogram line crossers. With MR paracetamol the initial presence of concentrations below the nomogram line within the designated 4-8 hour window appears to reject the need for antidote treatment only to cross the nomogram line at a later point in time, resulting in late initiation of antidote intervention.

To account for this, the Swedish guidelines have introduced a second, lower, line at which patients who have taken an overdose of MR paracetamol should be treated. This appears to suggest that the Swedish guidelines are more conservative than those currently established in Australia and New Zealand. However, this is not the case because the Swedish guideline relies on patient report (of whether IR or MR paracetamol was taken for the overdose) and a serum paracetamol concentration to be measured.

[redacted]

Table 8 (next page) provides a summary comparison of the key elements of the current MR paracetamol overdose protocols in Australia and New Zealand versus those in Sweden.

Table 8. MR paracetamol overdose protocols: Australia and New Zealand versus Sweden

	Australia & New Zealand	**Sweden**
Single toxic dose stated	Yes: 10 g	Yes: 140 mg/kg
Stated threshold for starting acetylcysteine treatment	Yes: overdoses of 10 g or 200 mg/kg (whichever is less)	No
Nomogram	Single line Rumack-Matthew Note: Previous versions had a second (lower) line for "high risk" patients. This was removed in the 2008 guidelines because it was deemed to introduce unnecessary complexity to clinical risk assessment (Daly et al 2008)	Two lines, the lower line to be used for assessing MR paracetamol overdose Note: Second line corresponds to the "high risk" line previously removed from the Australia & New Zealand guidelines
Serum paracetamol measurements	Yes: 4 and 8 hours post-ingestion	Yes: 4, 6, 12 and 18 hours post-ingestion
Blood sampling before initiating acetylcysteine	Not required if the ingested dose is above 10 g	Yes: due to potential for acetylcysteine to cause false low values for serum paracetamol

[redacted]

[redacted]

11 Practical differences between the paracetamol overdose guidelines in different countries

Overdose guidelines designed to specifically address the considerations required with MR paracetamol have been in place in Australia since its first launch in this market in 2001. Thus, guidelines to minimise the risk for hepatic injury following intentional or

[redacted]

accidental overdose with MR paracetamol are already established. However, two key questions remain:

- How are they different from those used in Sweden?
- Do they meet current best-practice guidance?

11.1 The established Australian overdose guidelines are based on different principles to those used in Sweden

The paracetamol overdose guidelines used in Sweden, which led to the PRAC referral in 2016, are considered inadequate. As previously shown in the Salmonsson et al publication, the Swedish guidelines can lead to delays in treatment and/or put patients at risk of not being treated with the antidote (Salmonson et al 2018).

The crux of the current discussion therefore requires an understanding of how paracetamol overdose is managed differently in Australia. The Swedish guidelines state that antidote treatment (with acetylcysteine) should be given based on where a patient's blood level of paracetamol is relative to a line on a chart (called a nomogram). In contrast, the Australian paracetamol overdose guidelines state that antidote treatment (with acetylcysteine) should be given to all patients who have ingested a paracetamol dose >10 g (Chiew et al 2015), irrespective of whether it is a modified-release paracetamol or an immediate-release paracetamol.

These two different approaches can be called a "blood level approach" (used in Sweden) and a "paracetamol dose approach" (used in Australia). The differences between these two approaches and their consequences in terms of their ability to minimise the risk for hepatic injury following intentional or accidental overdoses are summarised below, specifically in relation to Australia and Sweden.

Sweden: Blood level approach	**Australia: Paracetamol dose approach**
• All patients presenting with a paracetamol overdose are required to have a blood test done before they are treated with the antidote. • Patients are only eligible to receive the antidote if the paracetamol level in their blood has reached a certain cut-off level on a chart. • There are two different cut-off lines, one for standard paracetamol and another one for modified-release paracetamol, which are applied depending on the paracetamol formulation taken.	• Treatment with the antidote is started immediately in all patients who have ingested more than 10g of paracetamol, irrespective of its formulation. • Patients who have ingested more than 10g of paracetamol are still required to have a blood test, but the result is effectively used to determine when to stop antidote treatment (not when to start it). • If overdose with modified-release paracetamol is suspected, additional blood tests are done to monitor response to extended treatment for the purposes of

[redacted]

stopping treatment.

- The **limitations** of this approach are

(1) Patients have to wait until they have the results of a blood test before they can start treatment with the antidote.

(2) The emergency doctor needs to know how much time has elapsed since the overdose was taken to properly interpret the results of the blood test.

(3) The emergency doctor needs to know which paracetamol formulation has been taken to decide which cut-off line to use.

(4) There may be a greater risk of harm if modified release paracetamol has been used versus immediate release paracetamol, should that not have been considered.

- The **benefits** of this approach are

(1) Patients are treated with antidote immediately and this is continued until their blood test results indicate it can be stopped.

(2) The emergency doctor does not need to know which paracetamol formulation has been taken to decide on an appropriate initial course of action.

(3) There is effectively no greater risk in having modified-release paracetamol versus immediate release paracetamol.

- **Well-established treatment guidelines for overdose with modified-release paracetamol are established in Australia.**
- **The Australian paracetamol overdose treatment protocol is based on a paracetamol dose principal and is different to that used in Sweden.**

11.2 The Australian guidelines already meet the EMA PRAC guidance on the management of modified-release paracetamol overdose

When European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) decided to suspend the licences in the EEA, it also recommended, as an interim measure, revised guidance for the management of MR paracetamol overdose. This revised guidance was provided via a direct healthcare professional communication (DHPC).

In the EU, the marketing authorisation holder for the respective medicinal product usually disseminates a DHPC, either at the request of a competent authority in a Member State or the Agency, or at the marketing authorisation holder's own initiative (EMA Guidelines, 2017). The content and presentation of a DHPC disseminated by the marketing authorisation holder should be agreed with the (local) competent authority.

The MR paracetamol DHPC (MR-APAP DHPC, 2018) was sent to healthcare professionals who treat patients with paracetamol overdose (e.g. Poison Information

[redacted]

Centres, emergency department hospital physicians, intensive care physicians, and general practitioners). Distribution commenced from the 19th March, 2018.††

The DHPC reinforced that protocols of blood sampling and treatment regimens (as used in the management of overdose with immediate-release paracetamol formulations) in many European markets (e.g. Sweden) are not adequate in cases of overdose with MR paracetamol. To address this, the letter provided five suggested adaptations to these standard protocols to improve the management of cases relating MR paracetamol:

1. Where overdose with ≥10g of paracetamol (or ≥150 mg/kg body weight in children) is known or suspected, or where dose is unknown, treatment with antidote (N-acetylcysteine (NAC) should be started immediately regardless of the initial serum paracetamol level since serum paracetamol level in acute overdose with paracetamol modified release (MR) 665mg tablets might peak up to 24 hours after ingestion.
2. Where <10 g of paracetamol have been ingested and time since ingestion is known, multiple serum paracetamol samples should be taken at suitable intervals (e.g. 4, 6, and 8 hours after ingestion). Additional samples should be considered if serum paracetamol concentrations are not declining to low level. If serum paracetamol levels exceed the treatment nomogram at any time point, treatment with antidote (NAC) is indicated.
3. If time since ingestion is unknown or serum paracetamol concentration cannot be obtained within 8 hours of the overdose, it is recommended that treatment with antidote (NAC) should be initiated without waiting for serum paracetamol concentrations to be available.
4. If NAC treatment has been initiated, it should be prolonged beyond the first 21-hour NAC course if paracetamol level remains above the limit of detection (or greater than 10 mg/L) or if ALT is increasing (greater than 100 U/L), and should be continued until paracetamol is below the limit of detection (or 10 mg/L) or if ALT is falling below 100 U/L.
5. Antidote should be dosed as recommended by the local Poison Information Centre (include local contact details: Phone + Website + Email).

   A comparison of the EMA PRAC suggested guidance and the wording in the current Australian guidelines has been undertaken (as detailed in the table below). All five of the EMA PRAC-suggested adaptations have already been accounted for in the existing Australian guidelines. As such, the current Australian paracetamol overdose guidelines already meet recognised best practice requirements.

†† Mandated distribution to EEA markets in which modified-release paracetamol was marketed at the time (Belgium, Denmark, Finland, Luxembourg, Portugal, Romania, Sweden).

[redacted]

PRAC guidance on MR paracetamol	Wording in current Australian guidelines
• Where overdose with ≥10g of paracetamol (or ≥150 mg/kg body weight in children) is known or suspected, or where dose is unknown, treatment with antidote (N-acetylcysteine (NAC) should be started immediately regardless of the initial serum paracetamol level since serum paracetamol level in acute overdose with paracetamol modified release (MR) 665mg tablets might peak up to 24 hours after ingestion.	• If more than 200 mg/kg or 10 g (whichever is lower) has been ingested, acetylcysteine treatment should be started immediately. Serum paracetamol concentrations should be taken at 4 hours or more post-ingestion (as with standard preparations) and repeated 4 hours later.
• Where <10 g of paracetamol have been ingested and time since ingestion is known, multiple serum paracetamol samples should be taken at suitable intervals (e.g. 4, 6, and 8 hours after ingestion). Additional samples should be considered if serum paracetamol concentrations are not declining to low level. If serum paracetamol levels exceed the treatment nomogram at any time point, treatment with antidote (NAC) is indicated.	• If less than a toxic dose is ingested (10 g or greater than 200 mg/kg (whichever is lower)), serum paracetamol concentrations may be used to determine the need for acetylcysteine. Serum paracetamol concentrations should be taken at 4 hours or more post-ingestion (as with standard preparations) and repeated 4 hours later. If either concentration is above the nomogram line, acetylcysteine should be commenced.
• If time since ingestion is unknown or serum paracetamol concentration cannot be obtained within 8 hours of the overdose, it is recommended that treatment with antidote (NAC) should be initiated without waiting for serum paracetamol concentrations to be available.	• In patients in whom a paracetamol concentration cannot be obtained until 8 or more hours after ingestion, acetylcysteine should be commenced immediately, if the reported dose exceeds the threshold for possible toxicity. • If the time of ingestion is unknown, or the treating clinician is not confident of the history of ingestion, it is safest to treat the patient as a delayed presentation. Thus, the recommendation is to follow the > 8 hours scenario in Figure 2; that is to commence acetylcysteine.
• If NAC treatment has been initiated, it should be prolonged beyond the first 21-hour NAC course if paracetamol level remains above the limit of detection (or greater than 10 mg/L) or if ALT is increasing (greater than 100 U/L), and should be continued until paracetamol is below the limit of detection (or 10 mg/L) or	• Acetylcysteine may be discontinued if serial concentrations, taken 4 hours apart are below the nomogram line and are decreasing. Otherwise continue the full 21-hour course of acetylcysteine to its completion. • Near the completion of acetylcysteine the

[redacted]

if ALT is falling below 100 U/L.	patient should have a repeat ALT and paracetamol concentration. Acetylcysteine should be continued if the ALT is increasing (greater than 50 U/L) or paracetamol concentration is greater than 10 mg/L (66 μmol/L).
• Antidote should be dosed as recommended by the local Poison Information Centre (include local contact details: Phone + Website + Email).	*The Australian guideline provides the currently endorsed recommendations for antidote administration (per below). Note that the Poisons Information Centre contact details are provided on the poster version of the guidelines.* • It is recommended that dosing tables providing the required volume of 20% acetylcysteine by weight, are used to chart the volume required in each infusion. This precludes the need for calculations and decreases the potential for error. Such tables are found in the acetylcysteine product information and have also been reproduced in this guideline (Table 4).

- **The established Australian guidelines already incorporate all five of the PRAC best practice adaptations.**
- **Importantly, this reconfirms the position that the current protocol in place in Australia is considered best practice.**

11.3 The established Australian guidelines are based on similar principles to those used in Denmark and both meet the recent EMA PRAC guidance

The established Australian paracetamol overdose management guidelines are substantively similar to those used in Denmark; both rely on a paracetamol dose approach. In Denmark, there is a proactive overdose protocol for the treatment of overdose with paracetamol, where all patients are treated on suspicion of poisoning. Therefore, PRAC's justification for the recommendation to remove modified-release paracetamol from the market is not relevant in Denmark.

Importantly, as is the case in Denmark, the Australian guidelines are different to those in Sweden; they do not rely on establishing the paracetamol formulation taken or on blood test results before the antidote is given. The similarities between these two approaches are summarised below in relation to the PRAC guidance. Both sets of guidelines meet criteria

specified for best practice in the management of overdose with modified-release paracetamol, as determined by PRAC.

EMA PRAC guidance	Denmark: Paracetamol dose approach	Australia: Paracetamol dose approach
1. Start antidote immediately in cases where overdose with ≥10g of paracetamol (or ≥150 mg/kg body weight in children) is known or suspected, or where dose is unknown.	✓ YES: If more than 6 grams (child > 125 mg/kg) has been ingested treatment is initiated immediately The limit of 6 grams is an estimate.	✓ YES: If more than 200 mg/kg or 10 g (whichever is lower) has been ingested, treatment is started immediately.
2. Where <10 g of paracetamol have been ingested and time since ingestion is known, take multiple serum paracetamol samples. If serum paracetamol levels exceed the treatment nomogram at any time point, treatment with antidote (NAC) is indicated.	✓ YES: If paracetamol poisoning is suspected, the patient is admitted to hospital. Immediate intravenous NAC treatment is initiated.	✓ YES: Serum paracetamol concentrations should be taken at 4 hours or more post-ingestion (as with standard preparations) and repeated 4 hours later. If either concentration is above the nomogram line, treatment should be started.
3. If time since ingestion is unknown or serum paracetamol concentration cannot be obtained within 8 hours of the overdose, treatment with antidote (NAC) should be initiated without waiting for serum paracetamol concentrations to be available.	✓ YES: If paracetamol poisoning is suspected, the patient is admitted to hospital. Immediate intravenous NAC treatment is initiated.	✓ YES: If paracetamol concentration is unknown or cannot be obtained until 8 or more hours after ingestion, treatment is started immediately.
4. If NAC treatment has been initiated, it should be prolonged beyond the first 21-hour NAC course if paracetamol level remains above the limit of detection (or greater than 10 mg/L) or if ALT is increasing (greater than 100 U/L), and should be continued until paracetamol is below the limit of detection (or 10 mg/L) or if ALT is falling below 100 U/L.	✓ YES: NAC infusion for 36 hours is recommended as standard treatment. Duration is adjusted to the patient: Can be stopped after 20 hours, based on clinically determined parameters. Can be stopped after three consecutive blood samples (taken 6 hours apart) based on clinically determined	✓ YES: A full 21-hour NAC infusion course is recommended with this being prolonged based on clinically determined parameters.

[redacted]

	parameters.	
5. Antidote should be dosed as recommended by the local Poison Information Centre (include local contact details: Phone + Website + Email).	✓ YES: Specific guidance on NAC dosing is provided in the guidelines. Contact numbers provided.	✓ YES: Specific guidance on NAC dosing is provided in the guidelines. Contact numbers provided.

- **Unlike in Sweden, the Danish and the Australian/New Zealand paracetamol overdose treatment protocols are based on a paracetamol dose principal.**
- **The established Danish and Australian/New Zealand guidelines already incorporate the principal elements of the PRAC best practice adaptations.**
- **On the basis of these established guidelines, the Danish Medicines Authority has lifted the suspension and so re-instated the product licences permitting the sale of modified-release paracetamol.**

11.4 Local guidelines are established, adequate and reliable

Amongst patients who have had an overdose with MR paracetamol, longer time to initiation of acetylcysteine treatment is associated with a significant increased risk of hepatotoxicity (Chiew et al 2018).

Tan and Graudins recognised the potential for slow absorption of MR paracetamol and thus a delayed peak serum paracetamol concentration above the nomogram line, and concluded that the paracetamol treatment nomogram might not reliably predict hepatotoxicity (Tan et al 2006). The more recent 2015 update of the Australian and New Zealand guidelines offers further guidance in which serial paracetamol and alanine aminotransferase concentrations are used to determine the duration of acetylcysteine treatment in MR paracetamol overdose (Chiew et al 2015).

[redacted]

For this reason, treatment with acetylcysteine should be considered in anyone who is suspected to have taken an overdose of MR paracetamol or unknown paracetamol tablet of 10 g or more, rather than relying solely on measurements of serum paracetamol to determine whether or not to treat with acetylcysteine. This allows for a timely initiation of antidote, which is crucial for a positive response, as shown in the 2018 study by Chiew et al (see below).

This dose-based approach is consistent with the published Guidelines for the management of paracetamol poisoning in Australia and New Zealand (Chiew et al

2015). As previously stated (Section 3.1.3), analyses undertaken using data from GSK worldwide safety database has established the veracity of this approach in identifying patients in whom to initiate acetylcysteine:

[redacted]

Recently published data, based on a prospective review of 116 MR paracetamol overdose cases in Australia, reported that 21 cases (18%) developed hepatotoxicity (Chiew et al 2018). These patients had a significantly longer time to treatment than those who did not develop hepatotoxicity (16.5 versus 4.5 hours, $p<0.0001$). None of these patients required a liver transplant or hepatic encephalopathy, and all survived.

11.5 Sponsor's comment

The TGA has raised concern that the standard treatment protocol for paracetamol overdose based on the Rumack-Matthew nomogram may not be adequate to prevent liver toxicity following overdose with MR paracetamol.

The established treatment paradigm for paracetamol poisoning in Australia and New Zealand is that overdoses above 10 g should be treated immediately without waiting for results from paracetamol concentration analysis (Chiew et al 2015).

Analysis of the [redacted] supports that the standard protocol established in Australia is both adequate and highly effective in managing MR paracetamol overdose. This is corroborated independently with Australian data (Chiew et al 2018). In a 4.5 year prospective observational study, Chiew et al describe the clinical characteristics and outcomes in 116 patients who had ingested a toxic dose (> 10 g) of MR paracetamol over a period of 8 hours or less. Of these 116 patients 113 (97%) were commenced on acetylcysteine. The majority of those treated in a timely manner were spared toxicity: 21/116 (18%) patients developed hepatotoxicity; none of these patients required a liver transplant or developed hepatic encephalopathy, and all survived.

Having a second, lower nomogram line (as in the Swedish protocol) for use in MR paracetamol overdose cases does not identify and treat more patients than using a pre-set toxic cut-off dose (>10g) in conjunction with the single Rumack-Matthew nomogram line. However, the results from [redacted]), indicate that further additions to optimise the existing protocol for treatment of overdose with MR paracetamol may be warranted.

The current guidelines for the management of MR paracetamol overdose in Australia and New Zealand have been established since the launch of the product. Current data from [redacted] and from the Chiew et al 2018 analysis, alongside the very low reported incidence of overdose cases and an absence of treatment related fatalities with MR paracetamol in Australia, do not suggest an inadequacy of the current Australian and New Zealand guidelines. Rather they underscore opportunities to further refine the protocols for managing large (≥ 40 g) overdoses with MR paracetamol.

[redacted]

12 MR paracetamol: Benefit-risk profile when supplied as a Schedule 2 medicine

From the Submission:
"Up-scheduling MR paracetamol to Schedule 3 will provide an opportunity for pharmacists to counsel patients on the importance of not exceeding a dose of 6 tablets per day, whilst still preserving OTC access to these products."

The TGA seeks to determine whether it is appropriate to reschedule MR paracetamol from a Schedule 2 medicine to a Schedule 3 medicine. In this context, the primary differentiators between these two schedules are (1) the need for intervention by a registered pharmacist, (2) the need to determine that the medicine is suitable and (3) for information about the use/dosing of the medicine to be communicated.

To answer this question, a benefit-risk assessment (Table 9, following pages) has been undertaken that explores the appropriateness of MR paracetamol when made available to consumers as a Pharmacy Medicine (Schedule 2 medicine) and whether there is any compelling evidence, in the local market, to suggest that restricting access would further enhance that position. The outcome of this analysis suggests that a more restrictive access to MR paracetamol would be unlikely to improve on the established safety record of this product in Australia.

[redacted]

Table 9. Benefit-risk assessment on the appropriateness of MR paracetamol scheduling in Australia.

Benefit & Risk Considerations	Schedule 2 Medicine Rationale	Schedule 3 Medicine Rationale
Benefits		
Consumer access	Analysis of NSW PIC data and sales of MR paracetamol in 2016 demonstrates that, there has been: • 0.698 PIC inquiries per 1 million tablets sold. • 0.223 cases of toxic overdose per 1 million tablets sold. This extremely low ratio of calls to tablets sold suggests with a high level of confidence that consumers are able to use the medicine appropriately. **This is upwards 5-fold fewer PIC inquiries than occur in Sweden, which initiated the EMA PRAC referral.**	More restricted access is unlikely to substantially alter this number of calls. More restricted access may result in consumers reverting to using less preferred IR paracetamol, and thereafter to easier to access NSAIDs.
Clinical outcomes	MR paracetamol is well known to the medical community; Pharmacists and GPs support its use in this setting. MR paracetamol is a useful treatment for patients who are unable to take non-steroidal anti-inflammatory drugs due to tolerability or contraindications, without the need to adhere to the four-times daily dosing schedule required with IR paracetamol.	If more consumers revert to using IR paracetamol, clinical outcomes and compliance may be reduced as was demonstrated in the 2016 Australian study (Ortiz et al 2016).
Public health	No data to suggest that there is a public health issue with availability of MR paracetamol in this	No public health issues have been identified that might be improved with more restrictive access

[redacted]

	schedule. There has been no suggestion of a clinical concern regarding MR paracetamol medicines in Australia.	to MR paracetamol. While it could be argued that more restrictive access may reduce the potential for accidental overdose, it is unlikely to impact the determined stockpile who plans a suicide attempt. In the GSK safety database analysis (Table 3 Section 4.2.1) accidental overdose accounted for a minority of Australian cases (6/100) compared to intentional overdoses (67/100).
Consumer involvement	Risk mitigation measures, such as blister packaging, clear labelling and on-pack warnings, have been in place since MR paracetamol was first launched in 2001. For first time purchasers: Labelled instructions make it clear that the product should be dosed three times daily. Purchasers pay a premium to access the benefit of longer duration of action and convenience of 3 times daily dosing. For repeat purchasers: Will be familiar with the medicine and its three-times daily dosing schedule.	For first time purchasers: There is a perceived benefit to mandatory pharmacist advice to ensure the consumer is aware of dosing. For repeat purchasers: Unlikely to add value as already familiar with the medicine, but may add a barrier to accessing this medication.
Economic benefits	Economic benefit is unaffected as the costs of MR paracetamol are the same if no change to scheduling occurs.	Economic benefit is potentially affected as the costs of mandatory pharmacist advice/dispensing with have an associated cost reflected in the purchase price to patients.
Risks		
Overdose (intent unspecified)	NSW PIC shows that calls relating to MR paracetamol are substantially lower than are	The available data support an established level of safety and very low level overdose, more

[redacted]

	those for IR paracetamol. In 2016, 9.8% (818/8,341) of paracetamol calls related to MR paracetamol.	restricted access is unlikely to be able to improve on this proven track record.
Intentional misuse/overdose	NSW PIC shows that calls relating to intentional overdose with MR paracetamol are substantially lower than are those for IR paracetamol. • In 2015, 13.7% (263/1,915) of calls regarding intentional paracetamol overdose related to MR paracetamol. • In 2016, 12.8% (262/2052) of calls regarding intentional paracetamol overdose related to MR paracetamol. A review of the DAEN database found 40 entries relating to *overdose*; there was only 1 case report of an intentional product use issue and 1 case report of intentional overdose involving MR paracetamol in the time period (01 June 2001 - 17 Feb 2018)	The available data support an established level of safety and very low level of intended misuse/overdose, more restricted access is unlikely to be able to improve on this proven track record.
Accidental ingestion	The same review of the DAEN database found 2 case reports of accidental ingestions involving MR paracetamol in the time period (01 June 2001 - 17 Feb 2018).	The available data support an established level of safety and very low level of accidental misuse by minors, more restricted access is unlikely to be able to improve on this proven track record.
Worsened outcome	In the 13-year span (2005-2018) there have been 53 adverse events reported in the TGA ADRS database relating to MR paracetamol. • Of these, four list death as the outcome. One report indicates that paracetamol was likely to have played a role. • No reports provide definitive data to directly support death from overdose with MR paracetamol.	The available data support an established level of safety more restricted access is unlikely to be able to improve on this proven track record.

[redacted]

	There have been no deaths in patients who have developed hepatotoxicity subsequent to MR paracetamol overdose (Graudins 2014, Chiew et al 2018), and the number of toxic cases is proportionally lower compared to Sweden.	
Overdose management	The Australian and New Zealand overdose guidelines state that antidote treatment (with acetylcysteine) should be in all patients with an ingested dose >10 g (Chiew et al 2015). Recently published Australian data show that 113/116 (97%) patients with acute MR overdose received acetylcysteine, 21 (18%) patients developed hepatotoxicity, none of these patients required a liver transplant or hepatic encephalopathy, and all survived (Chiew et al, 2018). The management of MR paracetamol overdose in Sweden is very different to that in Australia. Data do not suggest an inadequacy of the current Australian and New Zealand guidelines. Additional modifications, to encompass multiple sampling and an extended period for monitoring appear to be warranted and should be investigated further but do not impact the scheduling status of this medicine.	The majority of overdose cases reported in the GSK safety database were from Sweden, even though access to MR paracetamol was more restricted (prescription only). Overdose management will proceed per guidelines irrespective of how the consumer accessed the medicine.

The only scenario where it could be suggested that some additional benefit might be conferred from mandatory pharmacist advice on dosing prior to dispensing is when a first-time user purchases the product.

However, as previously discussed, currently there is an up to 8-fold price premium between MR ($5.99 for 96 caplets) and IR ($0.69 for 100 tablets) paracetamol in a self-select pharmacy environment. It is counterintuitive to suggest that a patient who has self-selected the MR paracetamol product at such a considerable price premium (on the basis of it delivering longer (8-hour) pain relief and less frequent dosing (three-times a day versus four) might then forget the relevance of this dosing regimen. Therefore, it is unlikely, that a rescheduling to pharmacist only medicine (Schedule 3) would have a substantial enough benefit to out-weigh the down-sides of more restrictive access to the overwhelming majority of customers who use the product safely.

As is suggested in the literature (e.g. Chiew 2018) and from [redacted], refinements to the overdose guidelines may further enhance their utility in managing MR paracetamol overdose cases. However, overdose management will proceed per guidelines irrespective of how the consumer accessed the medicine, so such changes have minimal relevance to the scheduling of MR paracetamol.

Any change in scheduling status should be based on sound evidence that (i) the concerns are based on accurate evidence and (ii) that scheduling changes are the only mechanism for addressing these concerns. Neither of these are supported, suggesting that continuing focus on existing risk mitigation would be a more equitable solution than rescheduling in this case.

12.1 Practical solutions for equitable supply of MR paracetamol and provision of adequate risk minimisation strategies

Risk mitigation measures, such as blister packaging and on-pack warnings, that have been in place since the product was first launched in 2001 and have since been further supported with ongoing consumer and healthcare professional educational campaigns. In addition, label warnings and dosing instructions (e.g. maximum six tablets in 24 hours, *doses should be equally spaced throughout the day; the caplets must not be crushed*) have been in place on the sponsor's MR paracetamol packs in Australia since launch.

Additionally, the packs include the instruction: "If an overdose is taken or suspected, ring the Poisons Information Centre (AUST: 13 11 26; NZ: 0800 764 766) or go to the hospital immediately, even if you feel well because of the risk of delayed, serious liver damage if left untreated." Furthermore, all Panadol packs include a free call 0800 telephone number on the pack whereby consumers can seek advice directly from GSKCH, any such calls made would be treated in line with our established adverse event procedures.

12.2 Information, education and training available for Panadol Osteo (MR paracetamol)

The appropriate use of MR paracetamol for the management of mild to moderate pain associated with osteoarthritis in the self-select environment (e.g. Schedule 2 / Pharmacy Medicine) is further supported by a variety of information, education and training materials. These materials, described below, provide consumers and healthcare professionals with multiple avenues through which to access information to ensure the safety in use of MR paracetamol products. The primary product benefits – its longer (8-hour) duration of action and three-times daily dosing – are a consistently prominent feature in all of these materials. The up-take of the educational messages conveyed in these materials by consumers in Australia is established based on the very low number of calls to the PIC regarding the use of MR paracetamol medicines in comparison to the 2.7 billion tablets sold annually.

12.2.1 Consumer information and education

12.2.1.1 Current Product Labelling (pack)

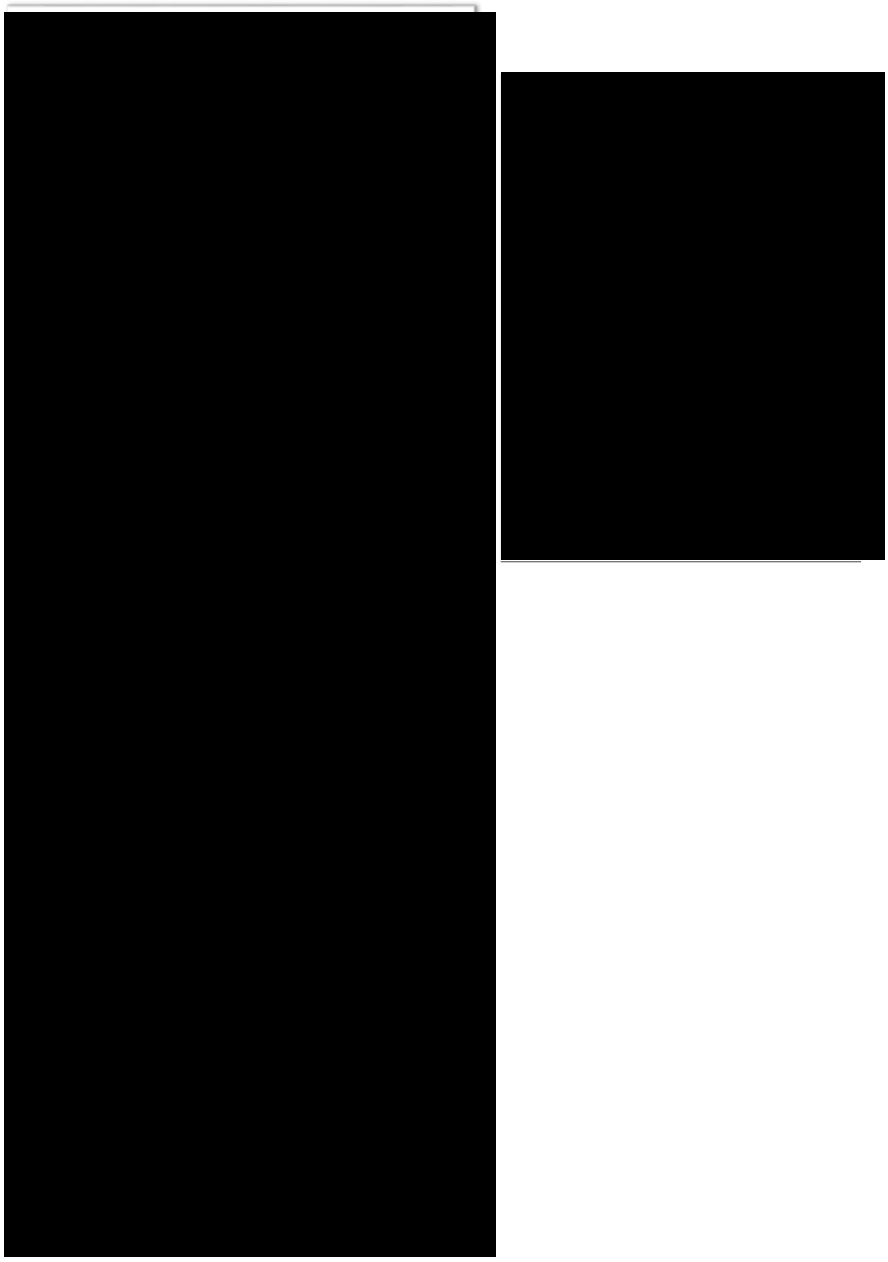
GSKCH is committed to patient safety and produces clear, consumer-oriented packaging and labelling. The outer carton of Panadol Osteo (665mg MR paracetamol) carries the core claim of up to 8-hour pain relief on the front and back of the pack. In addition, clear dosage instructions (based on performance-based labelling principles for which GSKCH has previously been awarded best practice) establish the parameters for product use:

- Two tablet dose
- 8 hour pain relief
- Maximum 6 tablets in 24 hours

Front of pack

[redacted]

Back of pack and end flap


[redacted]

12.2.1.2 Future Product Labelling (TGO92)

The TGA has introduced new labelling guidelines for OTC medicines (TGO92[‡‡]), which are changing medicine labels to make important information about medicines easier to find. Labelling requirements for Australian medicines are being updated after many years

[‡‡] Source: https://www.tga.gov.au/australias-medicine-labels-are-becoming-clearer

[redacted]

of consultation with industry, health professionals and the community. The changes help bring Australian medicine labels up to date and align them with international best practice. Importantly they are intended to help Australians to make more informed choices about their medicines and use them more safely.

The key elements are:

- medicine packs with active ingredients and dose strengths in larger font - active ingredients will be easier to find and differentiate
- Medicine information will be clearer - Most over the counter medicines will have critical health information in distinctive tables to help consumers use their medicine safely. The new rules mean that critical health information will always be displayed in a consistent order and will be easy to recognise.

[redacted]

One aspect of risk mitigation is to use package design to better help consumers differentiate between the different types of paracetamol products that are available over the counter for self-selection in Australian pharmacies. Better differentiation would be expected to have a two-fold impact on modified-release paracetamol – firstly it would aid those consumers who need the benefits of a long-lasting pain reliever to identify this as a suitable product for their needs and secondly, in the event of an overdose, it would be more apparent that the product taken contained modified-release paracetamol.

All Panadol packs incorporate evidence-based, consumer-focused labelling methodology to optimise the layout of information on the pack. Extensive work has been undertaken to help Australian consumers understand the differences between available products and to self-select the most appropriate Panadol product for their needs. [redacted]), state of the art consumer testing processes were used to determine the ease of navigation and differentiation of the new designs. This included:

(1) digital eye-tracking technology to evaluate what the consumer sees when they first view the pack on the shelf,

(2) shopping practices to measure the ease and time taken to locate a specific product on the shelf, and

(3) reactions to packaging to determine if consumers were still able to find key product information.

[redacted]

The results of comparative testing between the old and new pack designs (shown next page) have established improved ability amongst consumers to differentiate between the different Panadol packs and self-select products appropriately.

[redacted]

Thus, GSK continues its 17-year support of responsible, safe and appropriate self-selection and use of MR paracetamol by consumers in Australia.

12.2.1.3 Package leaflet

Since 2017, GSKCH has introduced product leaflets to all of its Panadol products in Australia (as part of a harmonised pack shared with New Zealand). As a result, Panadol Osteo is supplied with a paper product leaflet (CMI) in each pack, which provides detailed dosing information to reinforce dosing compliance.

The CMI is also available on the medicines.org.au website (http://www.medicines.org.au/product.cfm?ret=search&type=cmi&handle=gccpanos) in regular print, large print and as an oral recording free of charge.

The corresponding Product Information (PI) is also available on the medicines.org.au website (http://www.medicines.org.au/files/gcppanos.pdf).

This is notable as a CMI and PI are not mandatory for Schedule 2 or lesser scheduled medicines. However, globally, GSKCH has a long-standing ethic of working to a high level of consumer safety standards and has made these items available to consumers, Pharmacists and Doctors to support the responsible, safe and effective use of its products.

[redacted]

12.2.1.4 Online sources of Panadol Osteo specific product information available to consumers

GSKCH maintains the website (www.panadol.com.au). Within this website there is an individual product page which provides details on the use of Panadol Osteo: https://www.panadol.com.au/products/adults/long-lasting/panadol-osteo/

This product information page speaks explicitly to:

- 8 hours pain relief
- Only 3 doses required to provide 24 of pain relief
- Maximum 6 tablets in 24 hours

Additionally, GSKCH maintains an osteoarthritis focused consumer-facing website in Australia. It contains a product page that gives prominence to the 8-hour duration of action and the 3 times daily dosing of Panadol Osteo versus the four times daily dosing of regular paracetamol.

https://www.osteoactive.com.au/our-products/panadol.html

[redacted]

12.2.1.1 Mainstream Media Advertising to consumers

GSK advertises Panadol Osteo to consumers via mainstream media (TV, print). GSKCH is committed to giving prominence to the 8-hour duration of pain relief and the three-times daily dosing which differentiate MR paracetamol from IR paracetamol, as per the example in Figure 2 below.

Figure 2. Example screenshot from Panadol Osteo (665mg MR paracetamol) television advertisement, highlighting the duration of action and three-times daily dosing frequency

12.2.2 Pharmacy information and education

12.2.2.1 Panadol Osteo Training to Pharmacies

Training and appropriate, safe usage and recommendation of GSKCH products is paramount. At GSKCH we employ a pharmacy specific sales force of 31 territory managers (TMs). [redacted]

Once trained, the territory managers then carry out in Pharmacy training within their territory. This is either as part of their booked pharmacy visits (if time permits) or a separate training is booked with the pharmacy team including Pharmacists.

[redacted] The audience comprises a combination of Pharmacists and Pharmacy Assistants. [redacted]

12.2.2.2 Osteoarthritis online training initiatives for Australian Pharmacies

In addition to the above GSKCH-led training sessions, the GSKCH Expert team also collaborates with healthcare professional organisations to deliver education and training materials. The GSKCH Expert team manages healthcare professional education, accredited learning (e.g. CPD modules), field sales training, and healthcare professional communication at congresses/conferences.

[redacted]

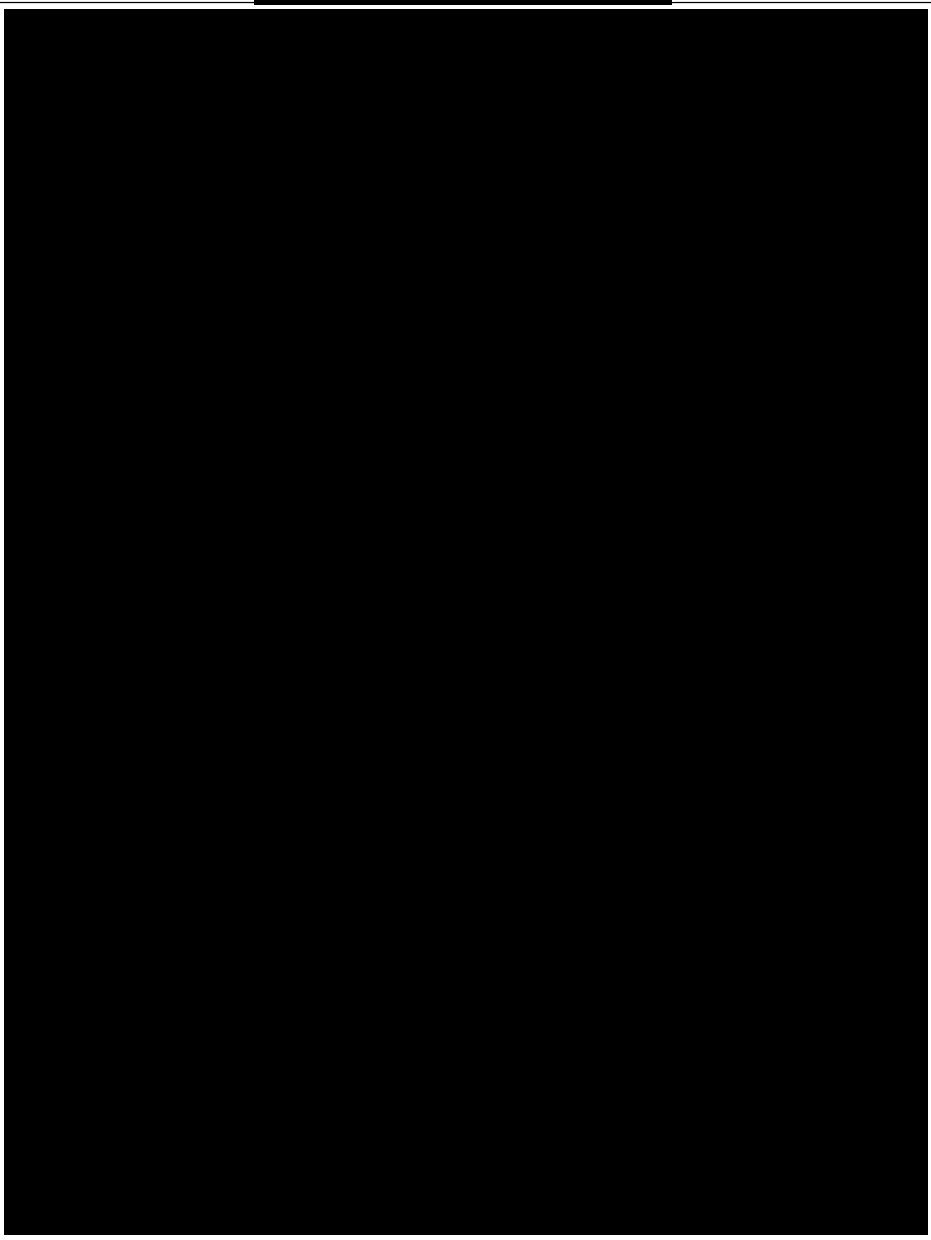
The current level of education and training of pharmacy teams would indicate the appropriate messaging is being given to consumers effectively, and this is further demonstrated by the small number of calls to seek information on appropriate usage of MR paracetamol over an 17-year period.

Nevertheless, GSKCH remains supportive of making ongoing training readily available through [redacted] professional bodies in support of responsible, safe and appropriate self-selection and use of MR paracetamol by consumers.

12.2.2.3 Panadol Osteo print based advertising for healthcare professionals

Promotion of Panadol Osteo to health care professionals is underpinned by core messages that are supported by the product's strong clinical rationale (three-times daily dosing) and established favourable risk-benefit profile when used to manage pain associated with persistent conditions such as osteoarthritis. An example of the type of promotional advertising designed to educate healthcare professionals on the core benefits of Panadol Osteo is provided on the next page.

[redacted]



Based on the above, there is an extensive and established programme (both in prominence and frequency) of consumer information and training for pharmacists and pharmacy staff. When purchasing MR paracetamol, pharmacy staff are routinely trained and available to address consumers' questions, so as to address concerns and negate any need to reschedule MR paracetamol from Schedule 2 (Pharmacy Medicine) to Schedule 3 (Pharmacist Only Medicine).

13 Conclusion: GSKCH position

MR tablets, containing 665 mg of paracetamol, have been approved and marketed as a Pharmacy Medicine (Schedule 2 medicine) in Australia since 2001. The licensed indication on pack for MR paracetamol in Australia is "Relief of persistent pain associated with osteoarthritis". These products are supplied in blister packs, predominantly containing 96 tablets.

A proposal is being considered to (1) correct the terminology in the Poisons Standard from 'slow release' paracetamol to 'modified release' paracetamol and (2) reschedule modified release paracetamol from Schedule 2 to Schedule 3.

GSKCH has no objections to the proposal to correct the terminology of MR paracetamol. However, recognizing that any change in scheduling status should be based on sound evidence that (i) the concerns are based on accurate evidence and (ii) that scheduling changes are the only mechanism for addressing these concerns, GSKCH opposes the proposal for the rescheduling of this product.

There is no indication that MR paracetamol, when used as directed on the label, increases the risk of hepatotoxicity-related hospitalization and there is no data to support the notion that MR paracetamol has any greater intrinsic risk overall than IR paracetamol at therapeutic doses. The available data continue to support the favourable risk-benefit profile of MR paracetamol.

Unlike Sweden, where MR paracetamol was available for use in acute and chronic pain states, in Australia, MR paracetamol is used primarily to treat OA pain. It is recognized that this formulation provides several benefits critical for the chronic-use required for OA pain management.

The current Australian guidelines for the management of paracetamol overdose, which include specific information regarding how to manage overdose with MR paracetamol including when to commence and discontinue treatment with the antidote (NAC) are optimal in the majority of overdoses cases. MR paracetamol overdoses can currently be successfully managed by careful monitoring of clinical presentation and laboratory measures. However, there is a recognised need for adaptation to ensure optimal treatment in the very small portion of patients who take a very large (≥40 g) overdose.

Such a large overdose is unlikely to occur as an accidental ingestion. Currently available data establish that in a year there are approximately 800 calls to the NSW PIC relating MR paracetamol (for any reason) and this has been investigated and extrapolated by TGA to reflect approximately 262 cases of toxic overdose (>10 g) with MR paracetamol in 2016 in all of Australia. Equating this data to the sales of MR paracetamol in 2016 (1,171,103,753 tablets):

- There were 0.698 PIC inquiries for any reasons per 1 million tablets sold.
- There were 0.223 cases of toxic overdose per 1 million tablets sold.

The rescheduling therefore disadvantages the many people who are already responsibly using this product to protect the small minority who opt to use it for deliberate self-harm.

The situation in Sweden is different to that in other markets, including Australia.

Unlike in Sweden, high incidence rates of overdose with modified-release paracetamol have not been observed in other markets. Using the number of calls to Poisons Information Centres as a proxy for all overdose cases (regardless of intent) and based on data available, in 2016-17 there was an average of:

- 0.698 inquiries per 1 million modified-release paracetamol tablets sold in Australia where modified-release paracetamol is a Schedule 2 Medicine
- 0.903 inquiries per 1 million modified-release paracetamol tablets sold in New Zealand where modified-release paracetamol is a Pharmacy Only (Schedule 2 equivalent) Medicine,
- 0.830 inquiries per 1 million modified-release paracetamol tablets sold in Denmark where modified-release paracetamol is a Prescription Only Medicine,
- 3.614 inquiries per 1 million modified-release paracetamol tablets sold in Sweden where modified-release paracetamol is a Prescription Only Medicine.

Data from Australia, Denmark and New Zealand provide compelling evidence that in countries where best practice overdose guidelines are established differences in medicines scheduling status does not have an impact on the incidence of overdose.

These points negate the proposition that rescheduling may pre-emptively prevent higher incidence rates that have been observed elsewhere.

Substantive risk mitigation measures are already in place to ensure the appropriate use of MR paracetamol. Safety measures, such as blister packaging and on-pack warnings, have been in place since the product was first launched in 2001 and these are further supported with consumer and healthcare professional educational campaigns. More recently, GSKCH has introduced leaflets in all of its paracetamol products to further support OTC self-select patient safety and education.

The majority of patients who use MR paracetamol in Australia do so responsibly and with little risk of accidental overdose. Current risk mitigation measures are adequate, there are no data to suggest that rescheduling MR paracetamol from its current Schedule 2 status to Schedule 3 will improve on this already favourable position.

14 References

Altman RD, Zinsenheim JR, Temple AR, et al. Three-month efficacy and safety of acetaminophen extended-release for osteoarthritis pain of the hip or knee: a randomized, double-blind, placebo-controlled study; *Osteoarthritis and Cartilage*, 2007; 15:454-461.

Andersen J, Clemmesen O, Dalhoff K, et al. Treatment of paracetamol poisoning. Danish Guidelines 2013.

Bacon, T. H., J. G. Hole, M. North, et al. Analgesic efficacy of sustained release paracetamol in patients with osteoarthritis of the knee; 2002 *Br J Clin Pharmacol* 53(6),629-636.

Bacon, T. H. G., T.J.; Darby-Dowman, A.; Hole, J.G. (2001). A novel sustained release oral paracetamol formulation: pharmacokinetics at steady state and relationship to clinical practice in patients with chronic pain. Australian Pain Society;**:** 63-64.

Benson, M., A. Marangou, M. A. Russo, et al. Patient preference for sustained-release versus standard paracetamol (acetaminophen): a multicentre, randomized, open-label, two-way crossover study in subjects with knee osteoarthritis; 2009 *J Int Med Res* 37(5),1321-1335.

Blamey, R., K. Jolly, S. Greenfield, et al. Patterns of analgesic use, pain and self-efficacy: a cross-sectional study of patients attending a hospital rheumatology clinic; 2009 *BMC Musculoskelet Disord* 10,137.

Brass, E. P., R. Lofstedt and O. Renn. Improving the decision-making process for nonprescription drugs: a framework for benefit-risk assessment. *Clin Pharmacol Ther*, 2011, **90**(6): 791-803.

Brass, E. P., R. Lofstedt and O. Renn (2013). "A decision-analysis tool for benefit-risk assessment of nonprescription drugs." J Clin Pharmacol **53**(5): 475-482.

Carr, A. Barriers to the effectiveness of any intervention in OA; 2001 *Best Pract Res Clin Rheumatol* 15(4),645-656.

Chiew, A. L., J. S. Fountain, A. Graudins, et al. Summary statement: new guidelines for the management of paracetamol poisoning in Australia and New Zealand; 2015 *Med J Aust* 203(5),215-218.

Chiew, A. L., G. K. Isbister, C. B. Page, et al. Modified release paracetamol overdose: a prospective observational study (ATOM-3); 2018 *Clin Toxicol (Phila)*,1-10.

Chiew AL, Isbister GK, Page CB et al. Modified-release paracetamol overdose: a prospective observational Study. *Clin Toxicol* 2017 55:5 (419).

Chiew AL, Isbister GK, Kirby KA, Page CB, Chan BSH, Buckley NA (Massive paracetamol overdose: an observational study of the effect of activated charcoal and increased acetylcysteine dose (ATOM-2), *Clin Toxicol*, 2017 DOI: 10.1080/15563650.2017.1334915

Chin CY, Khartoum M, Mohamed M et al. Evidence for persisting with treatment with paracetamol in patients with mild to moderate osteoarthritis of the knee. *Life Sci*, 2012; 9(3): 1131-1137.

Claxton, A. J., J. Cramer and C. Pierce. A systematic review of the associations between dose regimens and medication compliance; 2001 *Clin Ther* 23(8),1296-1310.

Daly, F. F., J. S. Fountain, L. Murray, et al. Guidelines for the management of paracetamol poisoning in Australia and New Zealand--explanation and elaboration. A consensus statement from clinical toxicologists consulting to the Australasian poisons information centres; 2008 *Med J Aust* 188(5),296-301.

Danish Medicines Agency. Annulment of suspension of marketing authorisation for Danish product license no. 03115, Panodil, GlaxoSmithKline, modified-release tablets 665 mg. May 2018 (original and translation).

Dart, R. C., J. L. Green and G. M. Bogdan. The safety profile of sustained release paracetamol during therapeutic use and following overdose; 2005 *Drug Saf* 28(11),1045-1056.

Graudins, A. Overdose with modified-release paracetamol (Panadol Osteo®) presenting to a metropolitan emergency medicine network: A case series; 2014 *Emergency Medicine Australasia* 26(4),398-402.

Graudins, A., A. Chiew and B. Chan. Overdose with modified-release paracetamol results in delayed and prolonged absorption of paracetamol; 2010 *Intern Med J* 40(1),72-76.

Graudins, A., H. N. Pham, C. Salonikas, et al. Early presentation following overdose of modified-release paracetamol (Panadol Osteo) with biphasic and prolonged paracetamol absorption; 2009 *N Z Med J* 122(1300),64-71.

GSKCH. Modeling and simulation analysis of paracetamol concentrations in the overdose setting. Internal report. 2017.

[GSK Clinical Study Summary 202195]. An Efficacy and Safety Study of Sustained-release Paracetamol in Subjects with Osteoarthritis. ClinicalTrials.gov Identifier: NCT02311881. 2016.

Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2012;64:465-74.

Hojer, J., H. Salmonson, G. Sjoberg, et al. [Overdose of modified-release paracetamol calls for changed treatment routines. New guidelines from the Swedish Poisons Information Centre]; 2016 *Lakartidningen* 113.

Hunter LJ, Wood DM, Dargan PI. The patterns of toxicity and management of acute nonsteroidal anti-inflammatory drug (NSAID) overdose. *Open Access Emerg Med*. 2011;3:39-48. Published 2011 Jul 6. doi:10.2147/OAEM.S22795

Laba, T. L., J. A. Brien, M. Fransen, et al. Patient preferences for adherence to treatment for osteoarthritis: the MEdication Decisions in Osteoarthritis Study (MEDOS); 2013 *BMC Musculoskelet Disord* 14,160.

Lehane, E. and G. McCarthy. Intentional and unintentional medication non-adherence: a comprehensive framework for clinical research and practice? A discussion paper; 2007 *Int J Nurs Stud* 44(8),1468-1477.

MR-APAP DHPC. *Paracetamol modified-release Dear Healthcare Professional Communication.* February 2018.

National Prescribing Service. Analgesic options for pain relief.; 2006 *NPS News* 47.

McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014;22:363-88.

NICE (National Institute for Health and Care Excellence): Osteoarthritis: care and management., 2014.

Machado GC, Maher CG, Ferreira PH, Pinheiro MB, Lin CW, Day RO, McLachlan AJ, Ferreira ML. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. BMJ. 2015 Mar 31;350:h1225.

Milder, T. Y., W. L. Lipworth, K. M. Williams, et al. "It looks after me": how older patients make decisions about analgesics for osteoarthritis; 2011 *Arthritis Care Res (Hoboken)* 63(9),1280-1286.

Ortiz, M., G. Calcino and F. Dunagan. Prescription usage patterns of two formulations of paracetamol in osteoarthritis: Australia-wide experience 2008-11; 2016 *Aust Fam Physician* 45(5),321-325.

Prior MJ, Harrison DD, Frustaci ME. A randomized, double-blind, placebo-controlled 12 week trial of acetaminophen extended release for the treatment of signs and symptoms of osteoarthritis. *Curr Med Res Opin*, 2014; 30(11): 2377-2387.

Punchak, S., L. I. Goodyer and F. Miskelly. Use of an electronic monitoring aid to investigate the medication pattern of analgesics and non-steroidal anti-inflammatory drugs prescribed for osteoarthritis; 2000 *Rheumatology (Oxford)* 39(4),448-449.

RACGP The Royal Australian College of General Practitioners. Guideline for the management of knee and hip osteoarthritis. 2nd edn. East Melbourne, Vic: RACGP, 2018

Richter, A., S. F. Anton, P. Koch, et al. The impact of reducing dose frequency on health outcomes; 2003 *Clin Ther* 25(8),2307-2335; discussion 2306.

Roberts, D. M. and N. A. Buckley. Prolonged absorption and delayed peak paracetamol concentration following poisoning with extended-release formulation; 2008 *Med J Aust* 188(5),310-311.

Salmonson, H., G. Sjoberg and J. Brogren. The standard treatment protocol for paracetamol poisoning may be inadequate following overdose with modified release

formulation: a pharmacokinetic and clinical analysis of 53 cases; 2018 *Clin Toxicol (Phila)* 56(1),63-68.

Schnitzer TJ, Tesser JR, Cooper KM et al. A 4-week randomized study of acetaminophen extended-release vs rofecoxib in knee osteoarthritis. *Osteoarthritis Cartilage*, 2009;17(1):1-7.

Schmidt LE. Age and paracetamol self-poisoning; 2005 *Gut* 54,686-690.

Schultz A, Petersen TS and Dalhoff KP. Poisonings with modified or prolonged release paracetamol tablets in Denmark.; 2017 *Clin Toxicol (Phila)* 55(5),208.

Smilkstein, M. J., G. L. Knapp, K. W. Kulig, et al. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985); 1988 *N Engl J Med* 319(24),1557-1562.

Stewart M, Cibere J, Sayre EC, Kopec JA. Efficacy of commonly prescribed analgesics in the management of osteoarthritis: a systematic review and meta-analysis. Rheumatol Int. 2018 Aug 17.

Tan, C. and A. Graudins. Comparative pharmacokinetics of Panadol Extend and immediate-release paracetamol in a simulated overdose model; 2006 *Emerg Med Australas* 18(4),398-403.

Tellerup, M., S. Forsberg and J. Hojer (2016). Paracetamol poisonings treated with two complete courses of N-acetylcysteine. 36th International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT). Madrid, Spain, Clinical Toxicology. **54:** 344-519.

Uppsala Monitoring Centre: Annual Report 2017-2017. Available from: https://www.who-umc.org/safer-use-of-medicines/uppsala-reports/uppsala-reports-archive/

VA/DoD. The non-surgical management of hip and knee osteoarthritis. US Department of Veterans Affairs and Department of Defense, 2014.

Yaligod, V., D. G. Raj, A. B. Sharma, et al. Dual release paracetamol in osteoarthritis of knee: a randomized controlled clinical trial; 2014 *J Clin Diagn Res* 8(11),LC11-15.

Yelland MJ, Nikles CJ, McNairn N et al. Celecoxib compared with sustained-release paracetamol for osteoarthritis: a series of n-of-1 trials. *Rheumatology (Oxford)*, 2007; 46(1):135-140.

Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2005;64:669-81.