

Modified Release Paracetamol

6-8 November 2018

Australian Government Department of Health

For further guidance in using this form, refer to the *Scheduling Policy Framework for Medicines and Chemicals 1 February 2015* (SPF), in particular refer to Chapter 4: GUIDELINES FOR APPLICATIONS AND INFORMATION REQUIREMENTS, available at (<https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>).

Guidance Notes

This application form is to be used for applications regarding scheduling, rescheduling or other proposals to amend the current Poisons Standard¹ (currently the *Standard for Uniform Scheduling of Medicines and Poisons*, the SUSMP), under section 52EAA of the *Therapeutic Goods Act 1989* (the TG Act).

The applications must be submitted electronically to the Medicines Scheduling Secretariat **or** the Chemicals Scheduling Secretariat (see relevant contact details at Part 5). The Scheduling Secretariats will acknowledge receipt of the electronically-submitted application form to the email address provided by the applicant.

Please note that any proposal to amend the Poisons Standard in respect of the requirements for **agricultural or veterinary chemical uses**, including those affecting labelling or packaging must be made through the APVMA (via the Office of Chemical Safety Assessment)(<http://www.apvma.gov.au>).

This application form is **not** intended to be used for general communications with the Scheduling Secretariats, submission of pre-meeting comments to the expert advisory committees or public submissions following the publication of an interim decision.

Use of this application form will ensure that your application is in an acceptable format and therefore avoid possible delays in consideration of your application. Applicants are asked to please familiarise themselves with these Guidance Notes before completing the form.

Size and fonts

Prepare text and tables using margins that allow for printing on A4 paper. Times New Roman, 12-point font, numbered paragraph style is recommended for narrative text. Ten-point font is recommended for footnotes. These are recommendations only, however, and do not restrict the applicant when selecting the format most appropriate to their submission. Please ensure that information provided is directly relevant to the application's consideration.

Language

Information supporting an application must be in English. Where material is not originally in English, a copy in the original language and a full translation (certified as a true copy) should be submitted. Applications submitted containing any part of the application written in a language other than English without the necessary accompanying translation may not be accepted.

Confidentiality

Please indicate if your application:

- contains no material claimed to be commercial-in-confidence; or
- contains material claimed to be commercial-in-confidence for scheduling purposes.

¹ See Section 52A of the *Therapeutic Goods Act 1989*

(Applications, or parts thereof including applicant or company name which may be disclosed in a public notice, that are claimed to be confidential should be clearly marked as such and justifications provided. Applicants should be aware that applications may still be subject to access in certain circumstances including where required or authorised by law, e.g. under freedom of information law).

The Secretary (or delegate) will consider claims that material is commercial-in-confidence based on Chapter 6 of the SPF. For further information on Confidentiality, see Chapter 6 of the SPF: GUIDELINES FOR USE OF CONFIDENTIAL INFORMATION.

Privacy

Your personal information is protected by law, including the *Privacy Act 1988*. Further information about how your personal information will be handled is set out in the Department of Health Australian Privacy Principle Policy:

<http://www.health.gov.au/internet/main/publishing.nsf/Content/privacy-policy>).

General

This application form includes text in { }. Such text is for guidance only and should be deleted when preparing a submission, as can these Guidance Notes.

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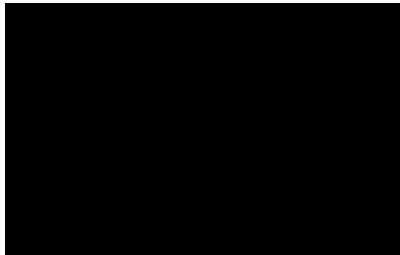
APPLICANT'S DETAILS

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DECLARATION

I Jane Cook, on behalf of applicant the Australian Government Department of Health:

- declare that the information provided in this application is true and current;
- undertake not to publicly disclose the notices of interim decision or final decision in respect of this application, until (if relevant i.e. following referral to an expert advisory committee) these documents are published pursuant to subsections 42ZCZP and 42ZCZS of the Therapeutic Goods Regulations 1990, respectively.



Name: Jane Cook

Date: 20 July 2018

PART 1 – SUMMARY OF THE APPLICATION

PROPOSED SCHEDULING / RESCHEDULING OR OTHER CHANGE TO THE POISONS STANDARD

1. The Australian Government Department of Health requests the rescheduling of slow release (MR) paracetamol, from Schedule 2 to Schedule 3, and the correction of terminology from slow release to modified release to accurately reflect the formulation of these products.

SUGGESTED SCHEDULING OR OTHER WORDING

The text in **red** is the proposed change.

Schedule 3 – Proposed new entry/amendment

PARACETAMOL:

- a) *when combined with ibuprofen in a primary pack containing 30 dosage units or less **except** when included in Schedule 2;*
- b) in modified release tablets or capsules.*

Schedule 4 – Proposed new entry/amendment

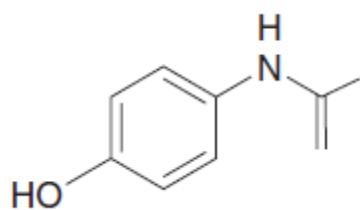
PARACETAMOL:

- a) *when combined with aspirin or salicylamide or any derivative of these substances **except** when separately specified in these Schedules;*
- b) *when combined with ibuprofen in a primary pack containing more than 30 dosage units;*
- c) *in **modified** release tablets or capsules containing more than 665 mg paracetamol;*
- d) *in **non-modified** release tablets or capsules containing more than 500 mg paracetamol;*
- e) *in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol;*
- f) *in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules except in schedule 2;*
- g) *in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules except when included in Schedule 2;*
- h) *for injection.*

SUBSTANCE SUMMARY

Paracetamol (also known as acetaminophen) raises the threshold to painful stimuli, thus exerting an analgesic effect against pain due to a variety of etiologies. It has analgesic and antipyretic effects similar to those of aspirin, but only weak anti-inflammatory effects.¹

Figure 1 – chemical structure and CAS number for paracetamol^{1,2}



CAS no. 103-90-2

MR paracetamol products are marketed in formulations containing 665mg of paracetamol. With the exception of one product, all available formulations are bilayer products, with an immediate release (IR) layer that is absorbed rapidly (similar to standard paracetamol formulations), and a sustained-release layer which allows for the gradual release of paracetamol from the tablet over a period of 8 hours. The relative proportions of these layers may vary between products. This formulation reduces the required frequency of dosing from four times per day to three times per day.³

Paracetamol is metabolised extensively in the liver and excreted in the urine mainly as inactive glucuronide and sulfate conjugates. The metabolites of paracetamol include a minor hydroxylated intermediate which has hepatotoxic activity. This intermediate metabolite is detoxified by conjugation with glutathione. However, it can accumulate following paracetamol overdose (more than 150 mg/kg or 10 g total paracetamol ingested) and if left untreated can cause irreversible liver damage and failure requiring liver transplant or resulting in death. MR paracetamol has an unpredictable pharmacokinetic profile requiring additional blood level monitoring and creating difficulties with treatment nomograms (an assessment based on serum paracetamol concentrations and hours since ingestion).¹

MR paracetamol is registered in Australia for the relief of pain and fever.

All MR paracetamol products available in Australia are currently schedule 2 (see part 2 of this application for a list of these products and more detail).

OVERVIEW

MR paracetamol tablets are constructed in two layers, an IR layer and a sustained release layer that gradually releases paracetamol over a period of 8 hours at normal doses. This reduces the frequency of dosing from four times per day to three, which may be more convenient for long term use in patients with chronic pain conditions such as osteoarthritis.³

Overdose with paracetamol, whether intentional or accidental, is common in Australia and in many other countries. Unless managed well there is a high risk of liver damage and death after paracetamol overdose. To this end there are comprehensive Australian and New Zealand guidelines on the management of paracetamol overdose which are based largely on serum paracetamol levels tested at various times after ingestion. The most important risk factor for liver damage and death after paracetamol overdose is delay beyond 8 hours of commencing treatment with acetylcysteine.

MR paracetamol has an unpredictable pharmacokinetic profile following overdose, may form pharmacobezoars (clumps of tablets) in the gut and can cause persistently high paracetamol concentrations for more than 24 hours after ingestion. Blood concentration can be erratic and difficult to predict due to the delayed absorption of the sustained release layer with double or delayed peaks above the treatment nomogram line.⁴ An overdose of MR paracetamol requires changes to clinical decisions and management (when and for how long acetylcysteine is required) due to the complex absorption of MR paracetamol into the body.⁴

MR paracetamol is currently a Schedule 2 (Pharmacy Medicine) product in Australia, sold over-the-counter (OTC) from pharmacies. It is difficult to accurately estimate use of MR paracetamol in Australia relying on PBS data, as the majority of use is from OTC sales and is therefore not reported. MR paracetamol was previously available as a general listing on the Pharmaceutical Benefits Scheme (PBS) for the indication of osteoarthritis pain, but this has been restricted to palliative care and Aboriginal and Torres Strait Islander patients since January 2016.

This issue has been considered by international regulators with the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recommending the suspension of marketing of MR paracetamol formulations in September 2017 and the New Zealand Medsafe Medicines Adverse Reactions Committee (MARC) recommending the up-classification of MR paracetamol to a pharmacist-only medicine in December 2017.^{5,6}

Chronic suprathreshold overdose is also thought to be not uncommon. This is likely largely due to confusion about the difference in dose between MR and IR paracetamol with the maximum dose being 6 tablets per day for the MR formulation rather than 8 tablets per day for IR. This confusion may be contributed to by the products being available adjacent to one another OTC without counselling/education provided at the point of sale. There is little evidence to suggest that this low level chronic toxicity is a cause of hepatotoxicity requiring treatment in otherwise well patients but remains best avoided and may be of concern in those with pre-existing hepatic impairment.⁴

The up-scheduling of MR paracetamol from Schedule 2 to Schedule 3 'Pharmacist Only' is a regulatory option in Australia that will help to ensure appropriate patient counselling on correct dosing and the risks associated with overdose, whether intentional or accidental.

PART 2 – BODY OF THE APPLICATION

BACKGROUND

Current Australian scheduling of MR paracetamol

MR paracetamol is currently a Schedule 2 (Pharmacy Medicine) product in Australia, and therefore sold OTC from pharmacies. According to the Poisons Standard⁷, a Schedule 2 medicine should be available from a pharmacy or, where a pharmacy service is not available, from a licensed person. This means that any pharmacy salesperson may conduct the sale, without the specific requirement to consult the pharmacist for advice.

Historical context

MR paracetamol was first entered in the Australian Register of Therapeutic Goods (ARTG) on 24 April 2001 as Panadol Extend.

There are 26 MR paracetamol products currently entered in the ARTG. The table below summarises the products currently registered in Australia, and their Australian sponsors.

Table 1 – MR paracetamol products available on the ARTG

Tradename	Sponsor
Panadol Osteo Duatrol Osteo GSK Paracetamol Osteo Panadol Back & Neck Long Lasting	GlaxoSmithKline Consumer Healthcare
Osteomol	Pharmacor
Chemist's Own Osteo Relief	Arrow Pharma
APO Health Osteo Relief ChemMart Pharmacy Osteo Relief Pharmacy Choice Osteo Relief ChemPlus Osteo Relief Discount Drug Stores Osteo Relief Amcal Osteo Relief Paracetamol Blooms The Chemist Osteo Pain Relief Terry White Chemists Osteo Relief	Apotex

Pharmacy Care Osteo Relief APO-Osteo Paracetamol APO-Paracetamol XR Apotex-Osteo Paracetamol Apotex-Paracetamol XR	
Genpar Paracetamol XR GXP Paracetamol XR AH Paracetamol XR	Generic Partners
Paracetamol Beximco 665mg MR Parapane Osteo	Beximco Pharmaceuticals Australia
Paracetamol Osteo-Tab	AFT Pharmaceuticals
Pharmacy Action Paracetamol Osteo	Lupin Australia

DETAILED CLAIMS AGAINST THE REQUIREMENTS OF THE SCHEDULING POLICY FRAMEWORK

PART 2.1 CRITERIA WHICH MUST BE ADDRESSED – PROPOSALS TO CHANGE PART 4 OF THE POISONS STANDARD – SCHEDULING OR RESCHEDULING OF SUBSTANCES

(A) RISKS AND BENEFITS ASSOCIATED WITH THE USE OF A SUBSTANCE

Risks of MR paracetamol

Paracetamol overdose can result in liver failure requiring liver transplant and may be fatal if not treated appropriately in a timely manner. Overdose with MR paracetamol poses risks over and above that of IR paracetamol due to its unpredictable pharmacokinetic profile, the consequences of which can be severe.

There are important differences in the availability, funding status and patient utilisation of MR paracetamol in Australia compared to other international jurisdictions including those that have recently taken regulatory action for these products.

Summary of risks of MR paracetamol:

1. Unpredictable and undefined pharmacokinetic profile
2. Severe consequences of overdose may be more likely to occur in patients who have ingested MR paracetamol
 - a. High potential for treating clinician to not be aware that a patient has ingested MR paracetamol
 - b. Unpredictable pharmacokinetic profile making monitoring and treatment difficult
3. Current best practice guidelines do not completely address MR toxicity
4. Large standard pack size facilitates consumption of higher dose.^{4, 7, 8}

See section (C) 'Toxicity and Safety of the Substance' for more detail.

Benefits of MR paracetamol

The sustained release formulation of MR paracetamol requires less frequent dosing and therefore may be more convenient for longer term use in patients with chronic pain conditions such as osteoarthritis. Its easy accessibility OTC means consumers do not need to visit their doctor in order to obtain a prescription. MR paracetamol is also relatively inexpensive. A search of the Chemist Warehouse website advertises packets of MR paracetamol 96 Caplets starting at \$5.99.⁹

Summary of Benefits of MR Paracetamol:

1. Three times daily dosing and reduction of tablet burden (compared with four times daily dosing of IR formulations);
2. MR paracetamol may be preferred by patients over IR paracetamol;
3. Use of opioid combinations or stronger opioids is higher in patients taking IR paracetamol, indicating that patients taking MR paracetamol may be less likely to move up the analgesic pyramid. (However, patients taking MR paracetamol are more likely to take non-steroidal anti-inflammatory drugs than those taking IR paracetamol).¹⁰⁻¹²

(B) THE PURPOSES FOR WHICH A SUBSTANCE IS TO BE USED AND THE EXTENT OF USE OF THAT SUBSTANCE

MR paracetamol is entered on the ARTG for the following indications:

- Effective relief from persistent pain for up to 8 hours.
- Effective for the relief of persistent pain associated with osteoarthritis and muscular aches and pains such as backache.
- Provides effective temporary relief of pain and discomfort associated with: headache, tension headache, cold and flu, period pain, toothache and pain after dental procedures.
- Reduces fever.

MR paracetamol is available as a restricted benefit on the PBS for the following indications:

- Analgesia or fever in palliative care patients intolerant to alternative therapy.
- Persistent pain associated with osteoarthritis Aboriginal or Torres Strait Islander patients.

MR paracetamol was previously available on the general PBS schedule for the indication of osteoarthritis pain, but this has been restricted to the categories above since 2016. It was recommended by the Pharmaceutical Benefits Advisory Committee (PBAC) that this listing be removed on 1 January 2016 following a review of PBS-listed medicines that were also available OTC.

MR paracetamol is available as a restricted benefit on the Repatriation Pharmaceutical Benefits Scheme (RPBS) for the following indication:

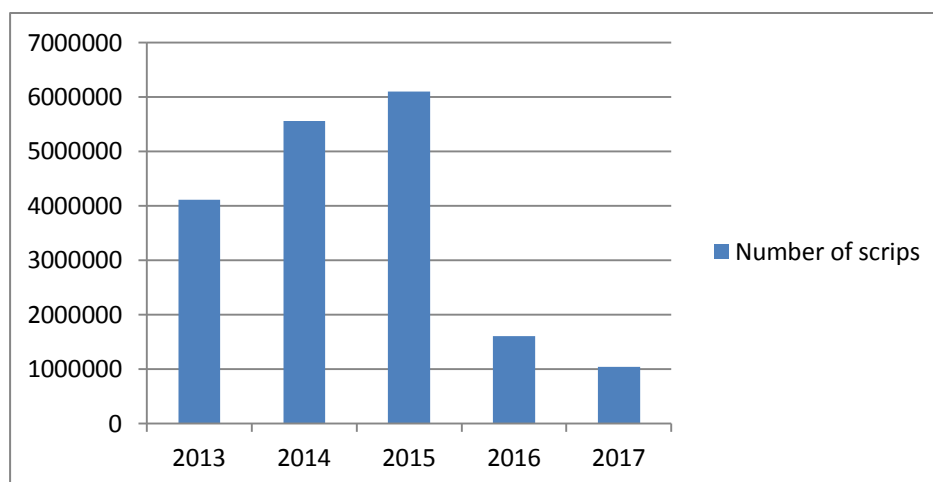
- Persistent pain associated with osteoarthritis.

Usage in Australia

It is difficult to accurately estimate use of MR paracetamol in Australia relying on PBS data, as a significant proportion of use is from OTC sales and therefore not reported.

A search of PBS data shows a significant decline in use from 2015 to 2016 which can be attributed to the change in PBS restrictions at that time. It may be that looking at Medicare data prior to 2016 gives a more accurate assessment of the true level of utilisation of MR paracetamol, most of which could be assumed to have shifted to OTC after January 2016 (see figure 2).

Figure 2 – Number of PBS prescriptions issued for MR paracetamol 2013-2017



It is also difficult to estimate how many people would be using MR paracetamol from these figures as the dose would vary from person to person, the maximum dose being two tablets, three times per day, or 6 tablets per day, but some patients may not require this much and may not use it every day.

Regardless, from these figures it can be reasonably concluded that MR paracetamol is a widely used medicine in Australia.

(C) TOXICITY AND SAFETY OF THE SUBSTANCE

Paracetamol overdose is common, whether it be deliberate self-poisoning, accidental paediatric overdose or repeated suprathreshold ingestion.⁷ In 2016, there were 8,341 cases of paracetamol overdose reported to the NSW PIC, and 818 (9.8%) of these involved MR products.⁸

As stated in the current *Guidelines for the management of paracetamol poisoning in Australia and New Zealand*, paracetamol (inclusive of IR and MR formulations) is involved in:

“...a large proportion of accidental paediatric exposures and deliberate self-poisoning cases and is the leading pharmaceutical agent responsible for calls to Poisons Information Centres in Australia and New Zealand. Paracetamol is also the single most commonly taken drug in overdoses that lead to hospital presentation and admission. Hepatic failure and death are uncommon outcomes, although paracetamol remains the most important single cause of acute fulminant hepatic failure in Western countries.”⁷

The highest recommended dose of paracetamol for adults is 1.3 g and the maximum daily dose is 4 g. A toxic dose is 10g or 200mg/kg (whichever is greater).⁴ The majority of patients who overdose take less than 30 g.⁴

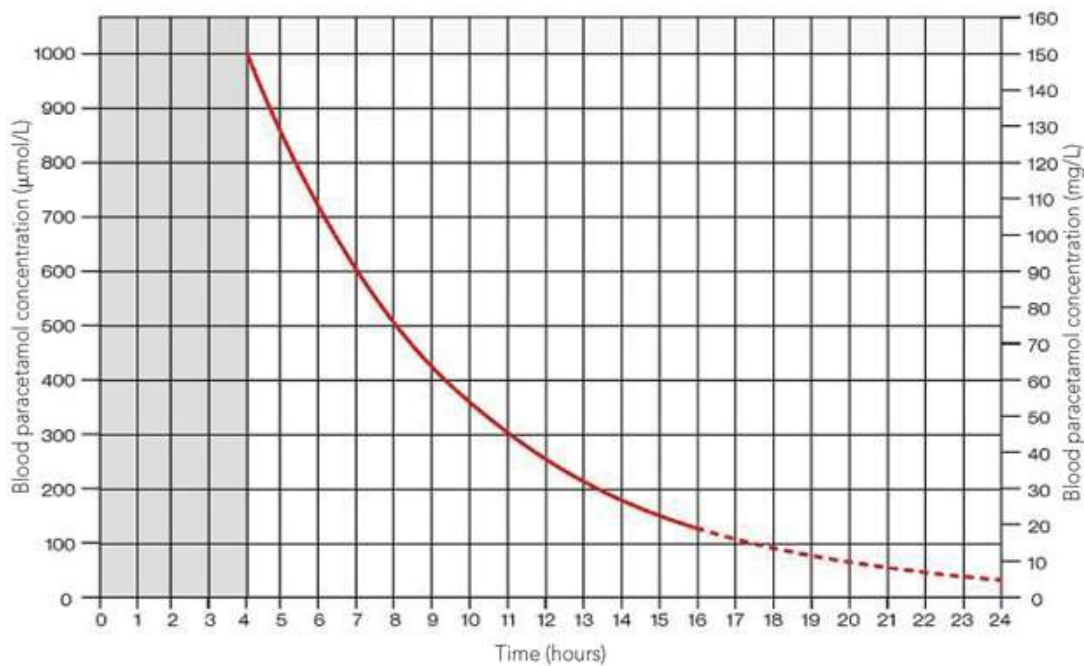
Immediate medical management is required in the event of an acute overdose of any paracetamol formulation, even if symptoms of overdose are not present. The complex manner by which MR paracetamol is released and absorbed into the blood stream has implications for clinical management: a complex pharmacokinetic profile; formation of pharmacobezoars in the gut (noting that the mode of MR includes gel formation in certain products); and high and prolonged paracetamol concentrations for greater than 24 hours. Treatment of overdose may include activated charcoal for gastric decontamination and the antidote acetylcysteine.

Overdose treatment

There are well established guidelines in Australia for the management of paracetamol overdose including with MR paracetamol. These were most recently revised in 2015 and are due to be updated in 2018.⁷ The treatment of paracetamol overdose is dependent on a number of factors and treatment given will vary accordingly. Key parameters include dose taken and time since exposure, if known. The mainstay of treatment is with acetylcysteine.

Whether acetylcysteine is administered depends on certain clinical parameters, including the use of the paracetamol treatment nomogram which plots the blood paracetamol concentration against time (see figure 3 below). Other investigations include measurement of liver function to assess for liver toxicity.⁷

Figure 3 – Paracetamol treatment nomogram⁴



The quantity of paracetamol consumed in the setting of an intentional overdose is commonly equivalent to one pack of IR paracetamol (10 – 12 g if the pack contains 20-24 x 500 mg tablets). The usual pack size of MR paracetamol (96 tablets) provides greater than 60 g if the whole pack is consumed during an intentional overdose.⁵ Available data suggest that dose ingested per kilogram bodyweight predicts the likelihood of hepatic damage.

In the event that the treating clinician is not aware that a patient has ingested a MR paracetamol formulation, the decision to give acetylcysteine, and for how long, may be delayed. This is significant because the most important risk factor for liver damage and death after paracetamol overdose is a delay of greater than 8 hours before commencing treatment with acetylcysteine.⁴ The optimal timeframe for treatment of a MR paracetamol overdose is variable and uncertain. Adherence to current best practice guidelines may not manage the risk of hepatic failure and death adequately even when the clinician is aware that MR paracetamol has been ingested.⁷

The best surrogate marker indicating the potential for hepatic injury following overdose is timed serum paracetamol concentration plotted on the nomogram, as published in the Australian and New Zealand guidelines.⁷ These guidelines acknowledge the undefined pharmacokinetic profile of MR paracetamol and the difficulties this presents when attempting to use the treatment nomogram which is based on IR paracetamol pharmacokinetics.⁴

The guidelines highlight the potential for slow absorption of MR paracetamol and subsequent delayed peak paracetamol concentration above the nomogram line. Recommendations for the management of MR paracetamol overdose differ from those for IR paracetamol overdose in a number of ways:

- Administration of 50 g activated charcoal, in cooperative adults, who can receive the dose within 4 hours of toxic MR paracetamol ingestion (>10 g or 200 mg/kg whichever is lower) is recommended (as with ingestion of large/massive (>30g) IR paracetamol ingestions).
 - In massive MR paracetamol overdoses, absorption may continue for up to 24 hours, so patients will likely benefit from activated charcoal even beyond 4 hours.
- Commence acetylcysteine treatment immediately (rather than waiting up to 8 hours for a serum paracetamol concentration with IR paracetamol ingestion).
- Serum paracetamol concentrations should be taken at 4 hours or more post-ingestion (as with IR preparations) and repeated 4 hours later.
- Near the completion of acetylcysteine treatment, the 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). Acetylcysteine can be continued at a rate of 100 mg/kg of acetylcysteine in 1000 mL of 5% dextrose over 16 hours.⁴

Australian Paracetamol Project

The Australian Paracetamol Project was a prospective observational study that recruited 116 patients from September 2013 to June 2017 from five clinical toxicology units in Australia and calls to the Poisons Information Centre in NSW and Queensland.⁷ It included patients over 14 years of age who ingested equal to or greater than 10g or 200 mg/kg (whichever was less) of MR paracetamol over a period of equal to or less than 8 hours, or developed acute liver injury following a MR paracetamol ingestion.⁴

The study found that of the 116 recruited patients, 80 (68%) had an initial paracetamol concentration above the treatment nomogram line (150mg/l at 4h) and a further 12 (10%) crossed the nomogram line after repeat paracetamol measurements, of which 5 crossed after two non-toxic levels 4 hours apart (see table 2 below).⁷ Six participants had a double paracetamol peak, with 3 occurring at greater than 24 hours after ingestion. Of the 113 patients (97%) that required treatment with acetylcysteine, 68 required prolonged treatment beyond the standard 20-21 hours. In 38 cases this was because of detectable paracetamol concentration at the completion of acetylcysteine, and in 29 patients it was due to ALT > 50 U/L (Australian recommendation for continuation).⁷

Table 2 – Modified release paracetamol overdose study: Patient demographic ingestion and treatment data⁷

Table: Patient demographic ingestion and treatment data.

	All patients (n = 117)
% Females	86 (74%)
Median age (years) (IQR)	36 (20–53.5)
Median weight (kg) (IQR)	75 (60–86)
Median dose ingested (g) (IQR)	31.9 (19.9–48.9)
Median dose ingested (mg/kg) (IQR)	0.440 (0.3–0.7)
Co-ingested gut slowing medications	24 (21%)
Co-ingested ethanol	29 (25%)
Median time to presentation (h) (IQR)	3 h (2–9)
Received activated charcoal	26 (22%)
Median time to activated charcoal (h) (IQR)	3.5 (1.3–5.2)
ALT at presentation not elevated (<50 U/l or at their baseline)	90 (77%)
Commenced on acetylcysteine	113 ^a (97%)
Median time to acetylcysteine (h) (IQR)	5 h (3.2–10)
<ul style="list-style-type: none"> • Completing at least 21 h of acetylcysteine • Adjustment to standard acetylcysteine dosing in the first 21 h of treatment • Prolonged acetylcysteine required beyond standard 20.5 h infusion 	103 (91%) ^b 27 (24%) ^b 68 (60%) ^b

^aOne patient ingested 7.98 g of MR paracetamol, had two non-toxic paracetamol concentrations and was not initially given acetylcysteine. Subsequently developed hepatotoxicity and acetylcysteine commenced at 96 h post ingestion.

^bPercentage of those commenced on acetylcysteine (n = 113).

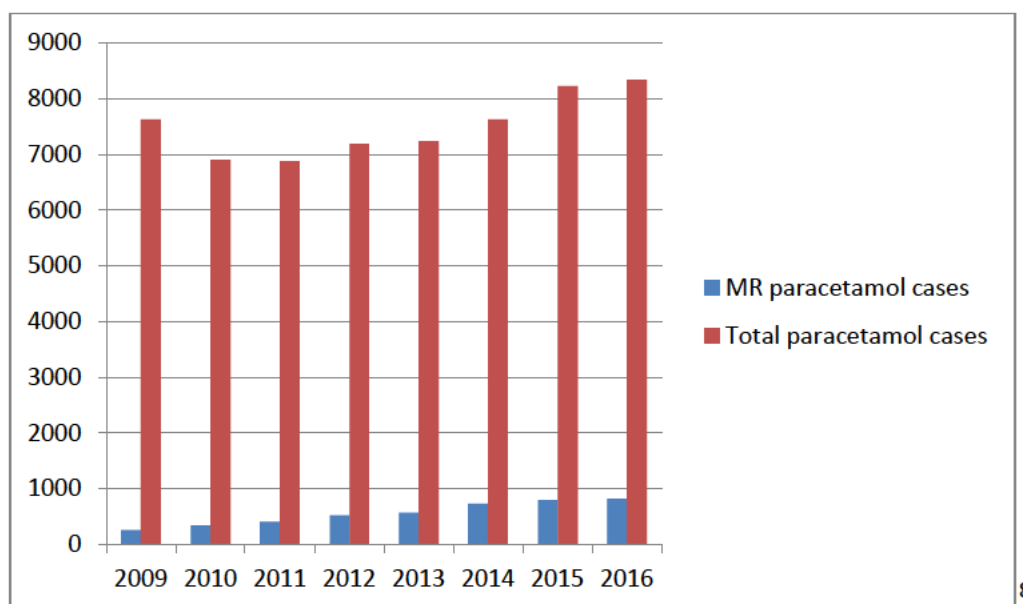
Twenty two (19%) of the participants developed hepatotoxicity, including 6 patients treated within 8 hours of ingestion. One patient developed hepatotoxicity despite ingesting <10g and having two non-toxic paracetamol concentrations.⁷ Significantly, the study authors concluded that better treatment strategies than the current Australian clinical guidelines for the management of MR paracetamol overdose are required if these products remain on the market.⁴

The Australian Paracetamol Project study⁷ confirmed several features of MR overdose that make patient management difficult: in 4% of patients, toxic levels requiring acetylcysteine occurred subsequent to two non-toxic levels four hours apart (which would usually permit discontinuation of acetylcysteine); 5% of patients had a double paracetamol peak; and the majority of patients required acetylcysteine treatment beyond the standard 21 hours. Twenty-one (18%) developed hepatotoxicity, including six treated within 8 hours of ingestion. One patient developed hepatotoxicity despite ingesting less than 10 g and having two non-toxic paracetamol concentrations. There were no fatalities.

NSW PIC data

Information provided by the NSW PIC suggests that MR paracetamol is implicated in 9.8% of all paracetamol overdoses (818 out of 8,341 in 2016).⁸ The annual number of calls made to the NSW PIC regarding overdose with MR paracetamol products, as well as any paracetamol-containing medicines, is presented in figure 4 below. It is important to note that the numbers shown in figure 3 for both the MR products and the total paracetamol cases include trivial overdosing, chronic overdosing and childhood poisonings. Acute overdose with greater than 10g of MR paracetamol is far less common. Note that the number of cases related to MR paracetamol is a small proportion of overall cases but is increasing.

Figure 4 - Annual number of calls made to NSW PIC regarding paracetamol overdose



Call to the NSW PIC pertaining specifically to intentional paracetamol overdose in 2015 and 2016 are presented in table 3 below. Approximately half of these are known to be overdoses of greater than 10g. Calls to the NSW PIC represented about half of all calls to poisons centres in Australia. Extrapolating the NSW PIC data for toxic MR overdoses to the whole population would therefore yield approximately 260 cases per year, based on 2015/2016 data.

Table 3 – Annual number of calls made to NSW PIC regarding intentional paracetamol overdose

	MR preparations	Total paracetamol (single ingredient preparations)
2015	263	1,915
2016	262	2,052

(D) DOSAGE, FORMULATION, LABELLING, PACKAGING AND PRESENTATION OF A SUBSTANCE

MR paracetamol is available as 665mg caplets in blister packs of 96 caplets. The packs of 96 are often sold in a quantity of two, as a total of 192 caplets, to provide one month’s supply.

The recommended dose is 2 caplets three times per day (every 6 to 8 hours), with a maximum of 6 caplets in 24 hours. MR paracetamol is not recommended for use in children under the age of 12 years.

The 96 caplet packs of MR paracetamol available OTC on schedule 2 contain a total of 63.84g of paracetamol which is more than six times the amount required for a toxic ingestion. This is compared with the amount contained in the largest available OTC pack of IR paracetamol (100 x 500mg tablets) which is 50g, keeping in mind that most IR paracetamol packs sold are smaller.

The availability of large pack sizes of MR paracetamol OTC may increase the risk of impulsive overdoses involving large amounts of paracetamol occurring, as the quantity of tablets consumed will be dependent on the quantity of tablets available at the time. Although this risk exists for larger packs of IR paracetamol, absorption of this formulation is predictable therefore facilitating effective treatment (see section (C) 'Toxicity and Safety of the Substance' for more detail).

The Required Advisory Statements for Medicine Labels (RAMSL) No. 3 (2017) lists the following to be provided in consumer information for paracetamol products:

- *Adults: Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised to by a doctor.*
- And/or*
- *Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.*
 - *If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 131126, New Zealand 0800 764 766) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.*
 - *Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.*¹³

(E) POTENTIAL FOR MISUSE/ABUSE OF THE SUBSTANCE

See section (C) 'Toxicity and Safety of the Substance above'.

(F) ANY OTHER MATTER THAT MAY BE RELEVANT TO THE SCHEDULING OF A SUBSTANCE

International regulatory actions

The complexity of MR paracetamol overdose management was the basis for a recent decision by the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) to suspend all MR paracetamol products in the European Union (EU) in September 2017. The PRAC review was instigated by a referral from the Swedish Medical Products Agency in June 2016, after concerns were raised in a study published by the Swedish Poisons Information Centre (Swedish PIC) by Salmonson et al.¹⁴

Salmonson et al's analysis of pharmacokinetics and clinical outcome data from the Swedish PIC collected between 2009 and 2015 included 53 cases of MR paracetamol overdose with a median dose of 20g. Eleven patients had a serum alanine aminotransferase (ALT) above the reference range (ALT >50 IU/L) at 24 hours or later. Six out of eleven patients developed hepatotoxicity (ALT >1000 IU/L). No fatalities were recorded.¹⁴

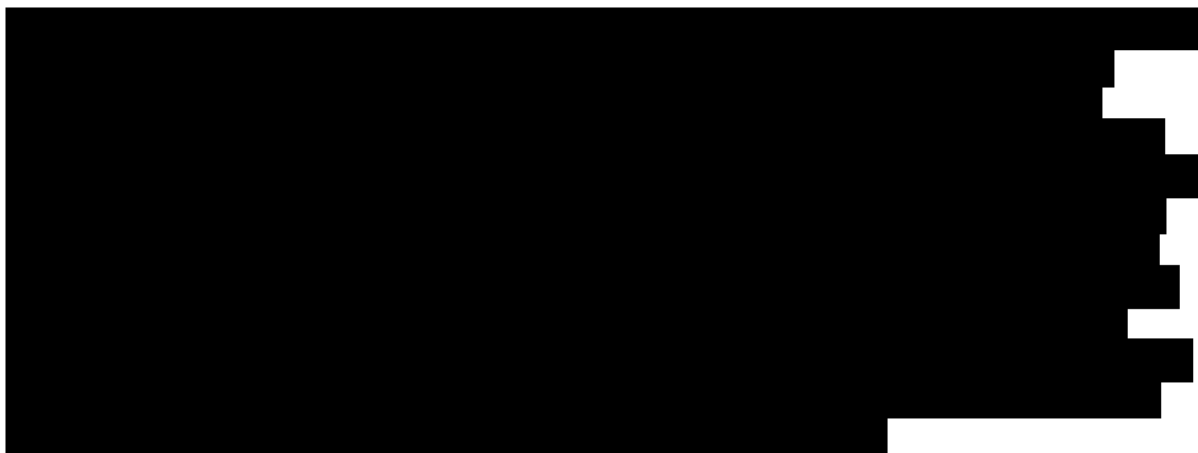
In Sweden there has been a dramatic upsurge in the use of MR paracetamol in recent years following intensive product promotion and public funding of the medicine. A single MR paracetamol product accounts for 40% of all paracetamol prescriptions in Sweden, and 21% of all calls to the Swedish PIC relating to paracetamol. During the study period, Sweden followed similar guidelines to those currently in place in Australia. The 2017 Swedish Guidelines were updated in response to this retrospective study by Salmonson et al.¹⁴ These updated clinical practice guidelines are more conservative than the current Australian guidelines, recommending more frequent monitoring of paracetamol concentrations over a longer period of time (4, 6, 12 and 18 hours after ingestion), a lower threshold for initiation of acetylcysteine treatment, and more aggressive treatment.

The PRAC considered that, in the event of MR paracetamol overdose, the usual treatment procedure for the IR products is not appropriate and that if the treating clinician is not aware that MR paracetamol has been taken, overdose might result in severe liver damage or death.⁵ The PRAC could not identify sufficient means to minimise the risk to patients, or a feasible and standardised way to adapt the management of paracetamol overdose across the EU to allow for treatment of cases that involve MR preparations. As a result, the EMA PRAC recommended that marketing of all MR paracetamol products be suspended in the EU.⁵

From the original PRAC report:

“For paracetamol MR tablets 319 spontaneous adverse event reports of overdose (OD) were reported since marketing authorisation. Of these 319 cases, almost all (98%) are from Sweden (67%) and Australia (31%). The majority of patients recovered or improved while 2 patients needed liver transplants. There were 5 fatal cases reported out of the 319 cases. Seven cases were reported to be unintentional but none of them were fatal.”⁵

This issue was discussed at the International Post Marketing Surveillance Teleconference (IPMS) in November 2017 held between the Therapeutic Goods Administration (TGA), the Food & Drug Administration (FDA) (USA), Health Canada, Health Sciences Authority (HSA) (Singapore), Medsafe (New Zealand) and Swissmedic (Switzerland). Information was sought from the TGA’s international regulatory partners regarding whether regulatory action was being planned in response to the PRAC recommendations, whether MR paracetamol was available in their jurisdictions, what the local prescribing requirements were, and whether there were any local guidelines for the management of paracetamol overdose (in particular MR paracetamol) currently in place.



New Zealand's MARC considered this issue in December 2017.⁶ The discussion examined the usage of these medicines and national PIC data. In New Zealand, MR paracetamol is not available to the consumer via public funding, and there are only two products approved for sale. Less than 1% (0.22%) of all paracetamol related inquiries to the New Zealand PIC relate to MR products, and the majority of these calls (77.4%) are related to therapeutic error rather than intentional overdose.⁶ The MARC further noted that of the calls relating to MR paracetamol, the majority were for therapeutic error. This is in comparison to less than a quarter of the calls regarding IR paracetamol to the New Zealand PIC being related to therapeutic error. From this information they concluded that consumers should receive counselling and advice on appropriate dosing.⁶

The MARC recommended that MR paracetamol be up-classified from a pharmacy-only medicine to a pharmacist-only medicine, in addition to a number of other risk minimisation strategies including updates to the datasheet and education to raise awareness on the management of overdose from MR paracetamol products and how this differs to overdose from IR products. The MARC concluded that up-scheduling these products to pharmacist-only would ensure that a pharmacist is involved at the point of sale to provide advice to consumers on dosing and thought that this would mitigate the risk adequately.⁶

The published MARC minutes do not canvas options of prescription-only scheduling, suspension of marketing or smaller pack sizes. The MARC also noted that the 2017 Swedish Guidelines for the treatment of MR paracetamol overdose are more cautious than the current Australian Guidelines.⁷

The MARC subsequently wrote to the authors of the Australian guidelines to request that the MR section of the document (currently based on a peak paracetamol level at eight hours) be reviewed, in light of Salmonson et al's study's finding that the peak dose of MR paracetamol can occur up to 24 hours after ingestion with persistently high levels for over 24 hours.¹⁴

The regulatory context for MR paracetamol in Australia falls somewhere between the Swedish and New Zealand examples. While the medicine was removed from PBS general listing for pain due to osteoarthritis on 1 January 2016, it is widely available OTC at the relatively inexpensive cost of approximately \$16 for a month's supply (at maximum dosage, 192 tabs).

The TGA received notification on 21 June 2018 of Denmark's Danish Medicines Agency's decision on 16 May 2018 to annul the suspension of paracetamol 665 mg prolonged-release tablets and not withdraw them from the Danish market citing the following reasons:

(In Denmark ...) "As we treat all overdosage with paracetamol based on suspicion of poisoning and do not await a response from blood tests, as well as adjusting the duration of antidote treatment to the individual patient, the Danish treatment of protocol is not considered to be insufficient. Based on this, the Danish Medicines Agency has now chosen to maintain depot-formulated paracetamol on the Danish market.", and

"In Denmark, we have a proactive overdose protocol for the treatment of overdosage with paracetamol, where all patients are treated on suspicion of poisoning. Therefore, PRAC's justification for the recommendation to remove depot-formulated paracetamol from the market is not relevant in Denmark."¹⁵

It is important to note that while the marketing suspension has been annulled in Denmark and MR paracetamol will remain available, it will still only be accessible with a prescription.

TGA Advisory Committee on Medicines (ACM) advice

Given the complexity of this issue, the TGA sought advice from the Advisory Committee for Medicines (ACM) in February 2018.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

See Appendix 1 for the full ACM meeting minutes on this issue.

TGA Adverse Drug Reaction System (ADRS) database summary

The reasons for overdose with MR paracetamol products in Australia are difficult to ascertain from the adverse event data currently available.

As at 25 June 2018 there were 53 adverse event reports in the TGA ADRS database relating to overdose (accidental and intentional), hepatotoxicity and liver injury, incorrect dosing and abnormal liver function with MR paracetamol, including 4 reports that list death as the outcome. Most reports do not list an outcome. Of the four reports of death, one indicates that MR paracetamol was highly likely to have played a role in the cause of death. There are no outcomes of fulminant hepatic failure reported (see Appendix 2 for more detail).

These reports were received between 2005 and 2018. Most reports do not specify whether the overdose was intentional or accidental.

The first report with death as the outcome (██████████) involved an ██████████ patient who was suffering from metastatic breast cancer. MR paracetamol was prescribed for chronic pain. The dose was reported as 2 x 665mg tablets 4 times per day (a prescribed overdose). The patient was known to have multiple liver metastases prior to the initiation of the drug. The patient developed abnormal kidney and liver function. At a later time the patient died, and it was noted she was also treated with buprenorphine patch and morphine for her pain. The temporal relationship between the initiation of MR paracetamol and the development of abnormal liver function is not clear from the case details, although it is likely that hepatic impairment predated her starting MR paracetamol, as she was prescribed the medication for pain related to her liver metastases. The causality assessment is complicated by the fact that the multiple liver metastases would likely have contributed to the development of abnormal liver function, although it is likely that the addition of a prescribed overdose of paracetamol would have worsened and/or accelerated this dysfunction. Given that the cause of death is not outlined in the case narrative, it is difficult to ascertain to what extent MR paracetamol was contributory. In light of this, the causality assessment has been determined as possible.

The second report with death as the outcome (██████████) involved a ██████████ who died at home from carbamazepine and citalopram toxicity. MR paracetamol was listed as an additional suspected medication but no further information was provided. It is unclear from the report whether paracetamol toxicity also contributed to this death, but it is possible.

The third report with death as the outcome (██████████) involved a ██████████ with a history of arthritis who died following a gastric ulcer haemorrhage. She was noted to be taking MR paracetamol three times per day but no further information was provided. From the information provided it is unlikely that paracetamol toxicity contributed to this death.

The final report with death as the outcome () involved a patient who died following multiple organ dysfunction, fall, seizure and abnormal electrolytes while taking MR paracetamol. The patient had been prescribed regular paracetamol for many years and at some time later was changed to MR paracetamol. The patient had a seizure shortly after moving to a nursing home and developed multiple organ dysfunction. The patient continued to decline and subsequently died. An autopsy was performed and the case was referred to the Coroner. The report states that *“the cause of death was multiple organ failure due to paracetamol toxicity (toxicology testing showed the level of paracetamol was 43mg/L which was in the toxic range).”* It is therefore probable that death was caused by paracetamol toxicity, although toxicity in this case was chronic rather than acute.

PART 2.2 CRITERIA WHICH MUST BE ADDRESSED – PROPOSALS TO CHANGE PARTS 1-3 OR PART 5 OF THE POISONS STANDARD

Not applicable to this application.

CONCLUSION

MR paracetamol would appear to provide little benefit over standard IR paracetamol other than less frequent dosing. 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 risk to the Australian population.

Data provided by the NSW PIC and the findings of the Australian Paracetamol Project study highlight the additional risks of hepatotoxicity with MR paracetamol compared with IR paracetamol. International regulators including the EMA and Medsafe have taken action on this issue with the EMA suspending sale of MR paracetamol in EU member countries altogether. Denmark has since annulled this suspension but it is important to note that MR paracetamol is only available there on prescription.

Noting that MR paracetamol is thought to be widely used in Australia to manage chronic pain in the elderly, the TGA considers that up-scheduling to S3 will provide an opportunity for pharmacists to counsel patients on the importance of not exceeding a dose of 6 tablets per day and provide a barrier to the impulsive purchasing of MR paracetamol for the purposes of taking an overdose, whilst still preserving OTC access to these products.

PART 3 – SUPPORTING DATA

SUPPORTING DATA SUMMARY

Appendix 1 – Advisory Committee on Medicines (ACM) 7 – modified release paracetamol and overdose – ratified minutes (TRIM D18-10791035)

Appendix 2 – Results of TGA ADRS search on 25 June 2018 for modified release paracetamol products and overdose (accidental and intentional), hepatotoxicity and liver injury, incorrect dosing and abnormal liver function (TRIM D18-10791037)

SUPPORTING DATA DETAILS

COPIES OF PAPERS REFERENCED

PART 4 – BIBLIOGRAPHY

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15. Letter from GlaxoSmithKline detailing the Danish Medicines Agency annulment of the suspension of marketing authorisation for paracetamol MR tablets 665mg, 21 June 2018. (TRIM D18-10791275).
16. Advisory Committee on Medicines Meeting 7, 2 February 2018 Agenda item 3.01 – Modified release paracetamol and overdose. Ratified Minutes for Modified Release Paracetamol. (TRIM D18-10791516).

PART 5 – SUBMITTING THIS APPLICATION

1. All applications to amend the Poisons Standard for medicine-related substances should be emailed to the *Medicines Scheduling Secretariat*:

Medicines.Scheduling@tga.gov.au

2. All applications to amend the Poisons Standard for chemical-related substances (non-medicines) should be emailed to the *Chemicals Scheduling Secretariat*:

Chemicals.Scheduling@health.gov.au