

# Reclassification of modified-release paracetamol to restricted medicine

## Purpose

The Medicines Adverse Reactions Committee (MARC) recommended at its meeting on 7 December 2017 that the Medicines Classification Committee (MCC) considers reclassifying modified-release paracetamol from pharmacy-only medicine to restricted medicine. This recommendation comes following recent regulatory action in Europe to suspend modified-release paracetamol products from the market due to the complexity of managing overdose with these products.

## Background

### Modified-release paracetamol

Modified-release paracetamol tablets are currently marketed in New Zealand in a formulation containing 665 mg of paracetamol, of which 69% is slow-release and 31% is immediate-release paracetamol [1-3]. The tablets are constructed in two layers: an immediate-release layer and a sustained-release layer. The immediate-release layer of the tablet is absorbed rapidly, similar to standard paracetamol formulations. The sustained-release layer contains a hydroxypropyl methylcellulose (HPMC) polymer, which rapidly hydrates to form a gel layer at the matrix periphery. Paracetamol is then released from the matrix by a combination of diffusion and erosion of the gel layer. With therapeutic dosing, the sustained release formulation allows for the gradual release of paracetamol from the tablet over a period of 8 hours, reducing the frequency of paracetamol dosing to three times per day, (*c.f.* four times per day for immediate-release paracetamol formulations) [3].

### Paracetamol overdose

Paracetamol is a widely-used non-narcotic analgesic and antipyretic medicine. When taken at therapeutic doses, paracetamol is considered the safest of all available analgesic agents, but in overdose it is potentially lethal [4, 5].

Paracetamol is involved in a large proportion of accidental paediatric exposures and deliberate self-poisoning cases [4, 6]. It is the leading pharmaceutical agent responsible for calls to the Poisons Information Centres in Australia and New Zealand. Paracetamol is the single most common drug taken in overdose leading to hospital presentation and admission, accounting for 22.4% of poisonings presenting to New Zealand public hospitals [6].

Paracetamol poisoning is the most common cause of acute liver failure in the developed world [1].

Overdose with modified-release paracetamol results in a biphasic and prolonged pattern of paracetamol absorption. The standard treatment protocol for paracetamol overdose based on the Rumack-Matthew nomogram may not be adequate to prevent liver toxicity following overdose with modified-release paracetamol [7].

### Previous discussions by MCC concerning modified-release paracetamol

Modified-release paracetamol 665 mg tablets were initially classified as prescription medicines in New Zealand. This classification was consistent with the guidelines for paracetamol-containing products, which at the time specified a 500 mg upper limit to the amount of paracetamol allowed in over-the-counter (OTC) tablets.

On 11 December **2001**, the MCC considered a company submission to reclassify modified-release paracetamol 665mg tablets as a pharmacy-only medicine. The MCC considered that the product should not be made available as a pharmacy-only medicine in view of:

- the difference in dosage from standard (immediate-release) paracetamol
- the potential for public misunderstanding about dose frequency (given the familiarity with immediate-release paracetamol dosing)
- the increased safety risk in cases of overdose.

The MCC recommended that these products remain prescription-only due to the potential confusion between modified- and immediate-release products that could result in unintentional overdosing. The MCC considered that professional intervention was necessary to ensure that consumers were made aware of the specific dosing regimen for modified-release paracetamol products. The MCC was also concerned that, following overdose, modified-release paracetamol would continue to be absorbed for a longer period than immediate-release paracetamol. Further details of the MCC's recommendation can be found in the minutes of the 26<sup>th</sup> MCC Meeting (Section 6.3), available at:

<http://www.medsafe.govt.nz/profs/class/Minutes/2001-2005/mccMin11Dec01.htm>.

In **2006**, with a view to harmonisation, the Australian National Drug and Poisons Schedule Committee (NDPSC) asked the New Zealand MCC to review its earlier recommendation, as tablets containing 665 mg of paracetamol had been classified as pharmacy-only (S2) medicines in Australia. On 9 June 2006, the MCC acknowledged that 665 mg tablets had been available in Australia for four years without evidence of significant problems related to overuse or overdose, but expressed ongoing concern that emergency rooms might not be aware of modified-release paracetamol products, and of the need to retest patients with equivocal blood paracetamol levels following overdose. The MCC agreed that there appeared to be no reason for New Zealand not to harmonise with the Australian classification for these products, but required an assurance from the company that the protocol for the treatment of paracetamol overdose would be revised to include management guidelines following overdose of 665 mg modified-release paracetamol. Further details of this recommendation can be found in the minutes of the 34<sup>th</sup> MCC Meeting (Section 8.1.4), available at:

<http://www.medsafe.govt.nz/profs/class/Minutes/2006-2010/mccMin9June06.htm>.

The revised classification as 'pharmacy only' was gazetted on 14 September 2006.

## Current Classification

The current classification criteria for paracetamol-containing medicines is shown in Table 1.

*Table 1 Current classification of paracetamol-containing medicines*

<b>Ingredient</b>	<b>Conditions</b>	<b>Classification</b>
Paracetamol	except when specified elsewhere in this schedule	Prescription
Paracetamol	in liquid form; in suppositories; in tablets or capsules containing 500 milligrams or less and in packs containing more than 10 grams and not more than 50 grams; in slow-release forms containing 665 milligrams or less and more than 500 milligrams; in powder form containing not more than 1 gram per sachet and more than 10 grams per pack	Pharmacy Only
Paracetamol	in tablets or capsules containing 500 milligrams or less and in packs containing not more than 10 grams; in powder form in sachets containing 1 gram or less and not more than 10 grams	General Sale

## Relevant products

To date, seven modified-release paracetamol products have been granted consent for distribution in New Zealand (Table 2). Currently only two of the seven approved modified-release products are marketed in New Zealand: Panadol Osteo Modified-release 665 mg tablets and Paracetamol Osteo-Tab Modified-release tablet.

*Table 2 Modified-release paracetamol 665 mg products with consent for distribution in New Zealand*

<b>Product name</b>	<b>Sponsor</b>	<b>Status</b>	<b>Approval date</b>
Panadol Osteo Modified-release tablet	GlaxoSmithKline Consumer Healthcare New Zealand Ltd	consent given	10/04/2008
Paracetamol Osteo-Tab Modified-release tablet	AFT Pharmaceuticals Ltd	consent given	10/01/2012
Panadol Back + Neck Long Lasting Modified-release tablet	GlaxoSmithKline Consumer Healthcare New Zealand Ltd	not available	10/04/2008
Paracetamol XR 665 mg Modified-release tablet	Apotex NZ Ltd	not available	25/09/2014

APO-Osteo Paracetamol 665 mg modified-release tablet	Apotex NZ Ltd	not available	25/09/2014
APO-Paracetamol XR 665 mg modified-release tablet	Apotex NZ Ltd	not available	25/09/2014
Osteomol 665 Modified-release tablet	Pharmbio Pty Ltd	not available	23/10/2014

## Recent international regulatory actions

### Europe

The European Medicine Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recently recommended that modified-release paracetamol products be removed from the European market.

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 [8]. The study reported on 53 cases of acute overdose with Alvedon (paracetamol) 665 mg modified-release tablets during the period 2009 to 2015. The authors noted that the exposure profile and subsequent clinical course following overdose with this product was unpredictable, the standard assessment and treatment protocol based on immediate-release paracetamol formulations was insufficient in the majority of these cases, and hepatic injury occurred in some cases despite timely treatment, (no liver transplants or deaths were noted as outcomes).

The PRAC considered that the advantages of a longer-acting product did not outweigh the complications of managing an overdose of this medicine. In many cases, the type of paracetamol formulation involved in an overdose may be unknown, making it difficult to determine appropriate treatment. The PRAC could not identify a way 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 modified-release preparations, and therefore recommended that the marketing authorisation for modified-release paracetamol-containing products be suspended.

The PRAC's recommendation was endorsed by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)<sup>i</sup>, and is now before the European Commission to issue a final legally binding decision that will be valid throughout the EU<sup>ii</sup>.

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<sup>i</sup> The CMDh is a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway.

<sup>ii</sup> More information on the PRAC's recommendation and the referral by the CMDh to the EC can be found on the EMA's website via the following link:

[http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Paracetamol-modified\\_release/human\\_referral\\_prac\\_000062.jsp&mid=WC0b01ac05805c516f](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Paracetamol-modified_release/human_referral_prac_000062.jsp&mid=WC0b01ac05805c516f)

## Scientific information

### Pharmacokinetics of modified-release paracetamol

The pharmacokinetics of a modified-release and an immediate-release paracetamol formulation have been compared by Tan *et al*, using a simulated overdose model in a cross-over study with seven healthy volunteers [2]. The mean paracetamol dose was 73 mg/kg actual body weight. The modified-release formulation produced a lower  $C_{max}$  (0.208 mmol/L  $\pm$  0.02 vs 0.48 mmol/L  $\pm$  0.02,  $P = 0.0001$ ) and  $AUC_{0-12\text{ h}}$  when compared with the immediate-release formulation, but the  $T_{max}$  was significantly delayed with the modified-release formulation compared to the immediate-release formulation (2.83 h  $\pm$  0.26 vs. 0.94 h  $\pm$  0.17,  $P = 0.0001$ ). Absorption was complete in all subjects by 4 h post ingestion in both study arms. There was no significant difference in the elimination  $t_{1/2}$  between the two formulations.

The lower  $C_{max}$  observed with the modified-release paracetamol formulation is attributed to elimination occurring during the absorption phase. Although the maximum concentration may be lower with the modified-release formulation, the time to maximum concentration ( $T_{max}$ ) is delayed due to ongoing absorption of the medicine. The paracetamol treatment nomogram may not, therefore, reliably predict hepatotoxicity following overdose with modified-release paracetamol formulations.

### Unpredictable clinical course following overdose with modified-release paracetamol Salmonson *et al*, Clinical Toxicology, 2017 [8]

***'The standard treatment protocol for paracetamol poisoning may be inadequate following overdose with modified-release formulation: a pharmacokinetic and clinical analysis of 53 cases'***

The Swedish Poisons Information Centre (Swedish PC) undertook a retrospective study of the pharmacokinetics and clinical outcome of acute overdose of the modified-release formulation after recognising an increasing number of such cases with prolonged, persistently high and unpredictable paracetamol levels. The study aimed to determine whether the recommended assessment and treatment protocol at the time was sufficient to manage overdoses with this formulation. The paper formed the basis of the referral by the Swedish Medical Products Agency to the PRAC in June 2016 regarding the benefit-risk profile of Alvedon 665 mg tablets, which has since resulted in suspension of the marketing authorisation for modified-release paracetamol-containing products in the EU.

The study examined a series of 53 cases of overdose with Alvedon (modified-release paracetamol) 665mg identified from the Swedish PC and hospital records for the period 2009 to 2015 were examined. Observed paracetamol concentrations in all 53 cases were plotted versus time.

Population PK-modelling revealed that the absorption of paracetamol was increasingly delayed with increasing doses of modified-release paracetamol. Double peaks in the serum paracetamol concentration became more evident with increasing doses. Persistent high serum levels for 24 h or more were observed in 10 of the 53 patients, the majority (9/10) had a reported dose of 50 g or more. In six of these 10 patients a second peak in the serum concentration was observed 8–19 h after intake, four of which had a reported dose of 50 g or more. The phenomenon of 'late nomogram line crossers' was observed in 10 patients, where the initial serum concentration, 4–8 h after reported intake, was below the nomogram but subsequently crossed the line.

Forty-three of the 53 cases studied received N-acetylcysteine (NAC) infusion, 34 of whom began the infusion within 8 hours of ingestion. In total, 11 patients had an ALT above the reference range at 24h or later, two of whom had non-toxic paracetamol concentrations recorded at 4-12 hours after ingestion. Six of these eleven patients developed hepatotoxicity (ALT>1000 IU/L). No signs of mitochondrial paralysis (coma, hypothermia, hyperglycemia) were reported, and no transplantations or fatalities occurred. Seven of the eleven patients with an ALT above the reference range were treated with NAC within 8 h of ingestion, of which three developed hepatotoxicity.

The PK analysis and PK modelling in this study demonstrated that risk assessment using only one or two serum samples 4–8 h after ingestion of modified-release paracetamol can be misleading, and may result in inadequate treatment and risk of hepatotoxicity. Repeated measurements of serum paracetamol are warranted even if treatment with NAC is ongoing, as persistently high serum concentrations for more than 24 h and double peaks can develop, especially after ingestion of high doses.

The authors concluded that the serum paracetamol-time profile following overdose with modified-release paracetamol is characterised by prolonged absorption with delayed maximum serum concentrations. Persistent high levels of paracetamol were observed, clearly correlated to increasing doses. The standard treatment protocol, based on experiences with immediate-release paracetamol, was insufficient to prevent development of liver damage especially in the cases with persistent high serum levels.

## New Zealand specific information

### CARM data

The New Zealand Pharmacovigilance Centre has identified one case of overdose in which modified-release paracetamol is possibly implicated.

**08286:** 74 y F reported to have hepatic enzymes increased approximately 5 months after starting *Panadol Osteo* (a modified-release 665 mg tablet). The daily dose was reported to be 8 DF, which equates to 5320g per day (33% above the recommended

maximum daily dose). Concurrent medicines were alendronate, ergocalciferol and calcium carbonate. The case was not serious and the outcome was unknown.

The daily dose reported in this case is 8 DF (i.e. 8 tablets). This dose is consistent with the recommended dose for immediate-release 500 mg paracetamol tablets/capsules (i.e. up to 2 tablets 4 times per day). The reported dose in this case suggests that the patient was not aware of the need to reduce the dosage frequency with modified-release tablets to no more than 3 times per day.

A more restrictive classification for modified-release paracetamol-containing products would require consultation with a health professional including advice on appropriate dosing, thereby reducing the risk of unintentional dosage errors.

### Poisons Centre data

NZ Poisons Centre data indicates that the number of cases of overdose with modified-release paracetamol in New Zealand is low compared to immediate-release paracetamol.

For the period 1 January 2008 to 8 October 2017, the National Poisons Information Centre received 13594 calls concerning paracetamol-containing products, of which 31 (0.22 %) concerned modified-release paracetamol products. Table 3 shows the categories of calls to the Poisons Centre for all paracetamol-containing products and for modified-release paracetamol products. Of note, the most common reason for calls concerning modified-release paracetamol was 'therapeutic error', which comprised 77.4% of calls for these products, compared to only 22.2% for paracetamol-containing products overall.

*Table 3. National Poisons Information Centre: reason for call*

Reason	All paracetamol		Modified-release paracetamol	
	n	%	n	%
Child Exploratory	5492	40.4	3	9.7
Therapeutic Error	3014	22.2	24	77.4
Intentional	2458	18.1	2	6.5
Unintentional	2394	17.6	2	6.5
Unknown	189	1.4		
Abuse	47	0.3		
<b>Total</b>	<b>13594</b>	<b>100</b>	<b>31</b>	<b>100</b>

Although the number of calls to the National Poisons Information Centre concerning modified-release paracetamol is low compared to the overall number of calls for paracetamol, it should be noted that approximately three-quarters of these calls were for 'therapeutic error' (e.g. incorrect dosage), compared to just over one-fifth of the calls for paracetamol overall.

This data indicates that confusion about the dosing of modified-release paracetamol products may lead to inadvertent suprathreshold dosing. Reclassification of modified-release paracetamol to 'restricted medicine' would ensure the involvement of a pharmacist

in the sale of the product, and that the consumer received advice on how often to take the medicine.

## Discussion

Modified-release paracetamol-containing products are being withdrawn from the European market following concerns about the complexity of managing overdose with these products.

Two modified-release paracetamol 665 mg products are available in New Zealand. Their current classification as a Pharmacy Only medicine means that any pharmacy salesperson may conduct the sale; consultation with a pharmacist, including advice on appropriate dosing, is not required.

Modified-release paracetamol constitutes a relatively small proportion of overall paracetamol sales in New Zealand. Consumers are more familiar with the immediate-release paracetamol products, which are widely available as General Sale medicines. Modified-release paracetamol 665 mg tablets contain 25 percent more paracetamol than immediate-release 500 mg products, and are formulated to provide a slower release of the active ingredient compared to immediate-release paracetamol. Consequently, modified-release paracetamol tablets should be taken no more than three times per day (c.f. four times per day for immediate-release paracetamol). Consultation with a pharmacist at the time of sale would ensure that the consumer is made aware of the correct dose interval for modified-release paracetamol.

Advice on the correct dosing by a pharmacist at the point-of-sale may help to reduce inadvertent suprathreshold doses with modified-release paracetamol 665 mg tablets. Furthermore, introducing a healthcare provider step in the process of obtaining modified-release paracetamol may help to reduce the likelihood that this product is purchased with the intention to overdose (i.e. less chance of an impulse purchase, and an increased differential in the relative accessibility of immediate-release products).

## Conclusion

Medsafe recommends that the MCC changes the classification of modified-release paracetamol 665 mg products to Pharmacist Only (restricted) medicine to ensure that consumers are advised of the correct dose of this medicine at the time of sale, thereby reducing the risk of inadvertent overdose. A restricted medicine classification may also reduce the ease of access, relative to immediate-release paracetamol, for intentional overdose, without limiting access to the product for its therapeutic purpose.

## References

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