Consumer Healthcare
82 Hughes Avenue
Ermington NSW 2115
Locked Bag 3
Australia

Tel +61 2 9684 0888
Fax +61 2 9684 1018
www.gsk.com | www.gsk.com.au

# INTENTION TO OBJECT TO A RECOMMENDATION MADE AT THE 60th MEETING OF THE MEDICINES CLASSIFICATION COMMITTEE, WELLINGTON, 26 APRIL 2018

## AGENDA ITEM:

## 6.5 Modified-release paracetamol – proposed reclassification from pharmacy-only medicine to restricted medicine (Medsafe)

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| Submitted by: | [redacted]<br>GlaxoSmithKline Consumer Healthcare, Australia and New Zealand |
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MCC Secretary
Medsafe
PO Box 5013
Wellington 6145

Sent by email: committees@moh.govt.nz

29 June 2018

**Re: Notice of intent to object to recommendation made at the MCC 60th Meeting**
**Agenda item 6.5: Modified-release paracetamol – proposed reclassification from pharmacy-only medicine to restricted medicine (Medsafe)**

Dear Sir/Madam,

At its 60th meeting (26 April 2018), the Medicines Classification Committee (MCC) discussed a proposal to reclassify modified-release 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, GlaxoSmithKline Consumer Healthcare (GSKCH) intends to object to this recommendation. The basis for our objection is that new information has become available since the MCC consideration that GSKCH considers to have the potential to cause the matter to be re-assessed. In addition, it appears from the minutes that some particularly pertinent points regarding modified release paracetamol may not have been considered in the meeting.

Our reasons for objection include the following.

1. Practical differences between the paracetamol overdose guidelines in different countries
2. Current situation in Denmark
3. [redacted]

1. Practical differences between the paracetamol overdose guidelines in different countries

The MCC meeting minutes state: *"The Committee considered the classification of this product overseas and the situation in Europe. Modified release paracetamol products have been suspended in Europe until a harmonised guideline on managing overdose can be established."*

The decision to suspend modified-release paracetamol products in Europe followed a complex Article 31 Referral procedure in the EEA which centred on concerns regarding modified-release paracetamol overdose in Sweden, where high rates of overdose and complexities managing such

paracetamol overdose cases had been identified as a safety issue. However, in giving its decision, the European Commission agreed that the suspension might be lifted at a national level if Marketing Authorisation Holders could provide evidence of proportionate, feasible and effective measures to prevent the risk of overdose and minimise the risk for hepatic injury following intentional or accidental overdoses.

The crux of the current discussion therefore requires an understanding of how paracetamol overdose is managed in different countries. This is explained specifically in relation to New Zealand and Sweden below:

| **Sweden: Blood level approach** | **New Zealand: 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.<br>• 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.<br>• 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.<br>• 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).<br>• If overdose with modified-release paracetamol is suspected, additional blood tests are done to monitor response to extended treatment for the purposes of stopping treatment. |
| • The **issues** with this approach are<br>(1) Patients have to wait until they have the results of a blood test before they can start treatment with the antidote.<br>(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.<br>(3) The emergency doctor needs to know which paracetamol formulation has been taken to decide which cut-off line to use.<br>(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<br>(1) Patients are treated with antidote immediately and this is continued until their blood test results indicate it can be stopped.<br>(2) The emergency doctor does not need to know which paracetamol formulation has been taken to decide on an appropriate initial course of action.<br>(3) There is effectively no greater risk in having modified-release paracetamol versus immediate release paracetamol. |

The paracetamol overdose guidelines used in Sweden, which led to the PRAC referral, are considered inadequate. As previously shown in the Salmonsson et al 2017 publication, the Swedish guidelines can lead to delays in treatment and/or put patients at risk of not being treated with the antidote.

Although PRAC decided to suspend the licences in the EEA, it recommended, as an interim measure, revised guidance for the management of modified-release paracetamol overdose (in a communication to healthcare professions; a DHCP letter). Importantly, this revised guidance for managing overdose with modified-release paracetamol released by PRAC incorporates the principal elements from the current and established guidelines that are already in place in New Zealand and Australia. This reconfirms the position that the current protocol in place in New Zealand is considered best practice.

This is new safety information because, at the time of the MCC's 60th meeting, the effective endorsement from PRAC of the current protocols in place in New Zealand was not considered.

2. Current situation in Denmark

As is the case in New Zealand, Denmark also has its own paracetamol overdose treatment protocol and decided it was adequate and appropriate to overturn the European Commission marketing suspension on modified-release paracetamol. On 16 May 2018, the **Danish Medicines Agency** announced an annulment of this marketing suspension – modified-release paracetamol therefore remains on the market.[1] 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 is different to that used in Sweden. Like the protocol in New Zealand, 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 overdose with modified-release paracetamol products to be an issue in this market. [redacted].

GSKCH has already provided data demonstrating a very low level of calls to the Poisons Information Centre in New Zealand. In the 10 years that modified-release paracetamol has been available in New Zealand, there have been 31 inquiries relating to this product. [redacted]

[1] Source: https://laegemiddelstyrelsen.dk/da/nyheder/2018/depotformuleret-paracetamol-forbliver-paa-markedet-i-danmark/

[redacted]. **This information is comparable to that observed in Denmark.**

GSKCH has already provided information about the paracetamol overdose management guidelines that are established in New Zealand. These guidelines are acknowledged locally as best practice by New Zealand toxicologists and widely used by the New Zealand A&E community. Importantly, as is the case in Denmark, the New Zealand 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 established New Zealand paracetamol overdose management guidelines are substantively similar to those used in Denmark; both rely on a paracetamol dose approach.**

The process to lift the marketing suspension on modified-release paracetamol is currently on-going in several other European countries. Key elements of this process include utilisation of the PRAC overdose guidance and discussion of risk mitigation strategies such as blister packaging and consumer education – all of which are elements that have been in place in New Zealand for over 10 years.

It is possible that the MCC may not have placed sufficient weight on the ability for current overdose treatment in New Zealand to manage modified release paracetamol, given the comment in the minutes that *"[t]here is a risk that paracetamol overdose may not be appropriately treated due to its slow release profile over time".* Since 2008, the New Zealand guidelines have included the management of modified-release paracetamol to ensure appropriate treatment.

While the MCC has been provided with information regarding the paracetamol overdose guidelines in Sweden and in New Zealand, they have not previously considered those in Denmark or taken account of the overdose guidance issued by PRAC. As such, the Committee has not had the opportunity to properly consider the safety implications of the current paracetamol overdose management guidelines available in New Zealand. In applying for this objection, GSKCH seeks to present this information to the Committee such that they can consider the new ruling from Denmark in context with the situation in New Zealand.

3. [redacted]

Our original submission provided a number of risk mitigation strategies that could be considered by the Committee. One aspect of risk mitigation is to better help consumers, and healthcare professionals, differentiate between products so that event of an overdose it is clear whether the product contained modified-release paracetamol.

In line with this, work has been undertaken to help New Zealand consumers understand the differences between available products and to self-select the most appropriate Panadol product for their needs. [redacted].

All Panadol packs incorporate evidence-based, consumer-focused labelling methodology to optimise the layout of information on the pack – [redacted]. To achieve this [redacted].

Concluding comments

The issues discussed by the Medicines Classification Committee were reflected in the minutes in terms of the "potential risks" for modified-release paracetamol products and were contextualised relative only to the situation in Sweden. Like Denmark, New Zealand is very different to Sweden in terms of both the volume of modified-release paracetamol overdose inquiries and established paracetamol overdose management protocols. GSKCH therefore asks that the recent regulatory decisions in Denmark are reviewed and taken into account before any final recommendations are made locally.

GSKCH retains its initial position that modified-release paracetamol has a favourable benefit-risk profile when supplied as a pharmacy-only medicine. The long-established overdose guidelines in New Zealand are considered global best practice and new updated product packaging has demonstrable ability to help consumers appropriately self-select based on the active ingredients.

Yours sincerely,

[redacted]
GlaxoSmithKline Consumer Healthcare, Australia and New Zealand