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GlaxoSmithKline Consumer Healthcare (GSKCH) Response to invitation for public comment on:

Delegate's Interim Decision ACMS Meeting, March 2019

Proposed rescheduling of modified release paracetamol from Schedule 2 (Pharmacy Medicine) to Schedule 3 (Pharmacist Only Medicine)

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Advisory Committee on Medicines Scheduling
Therapeutic Goods Administration

Sent via email: medicines.scheduling@health.gov.au

Re: ACMS Meeting March 2019
Item 1.5. Interim Decision in relation to paracetamol (modified release)

Background

Modified release 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 44 modified release 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.

At its March 2019 meeting the Advisory Committee on Medicines Scheduling (ACMS) considered a proposal to up-schedule modified release paracetamol from Schedule 2 (Pharmacy Medicine) to Schedule 3 (Pharmacist Only Medicine). This consideration had been prompted by a Therapeutic Goods Administration (TGA) review of the safety of modified release paracetamol in Australia, and subsequent advice from the Advisory Committee on Medicines (ACM), following an earlier decision by the European Medicines Agency (EMA) to suspend marketing of modified release paracetamol products in the European Union.

The ACMS had recommended the deletion of the current Schedule 2 entries for modified release paracetamol and the delegate's interim decision is to conform to this recommendation with a proposed implementation date of 1 October 2019. GlaxoSmithKline Consumer Healthcare (GSKCH) welcomes the opportunity to comment on this interim decision.

GSKCH position

In principle, GSKCH does not agree with the proposed up-scheduling of modified release paracetamol to Schedule 3. Some data were presented in the public submissions regarding the apparent increased use of this formulation in intentional overdose and the higher costs of managing overdose with this formulation versus standard paracetamol. However, overall the data does not support modified release paracetamol to be substantially less safe than other ingredients currently included in Schedule 2.

Based on this, it can be reasonably deduced that the biggest risk of harm with modified release paracetamol is amongst the small percentage of the population who choose to misuse the product rather any misuse by the vast majority of users of modified release

paracetamol who benefit from convenient access to this medicine through pharmacies around the country. We would argue that evidence in Australia, where the risk of adverse overdose outcomes have been effectively mitigated for the entire 18 years of Schedule 2 availability, speaks volumes in response to hypotheses raised alluding to unpredictable pharmacokinetics, potential pharmocobezoar development and the availability of large pack sizes.

We support the decision of the delegate in maintaining the continued inclusion of Schedule 3 paracetamol in Appendix H (a position also supported in the public comments of the Pharmacy Guild of Australia) and thus providing a means for necessary patient education and communication. On that basis, GSKCH does not challenge the interim decision to reschedule modified release paracetamol from Schedule 2 to Schedule 3, but we would like to raise and seek resolution of our concerns with the appropriateness of the proposed implementation date of 1 October 2019 for the change to take effect. We also request that consideration of provisions for labelling exemptions for existing stock be considered by the state and territory medicines regulators to avoid supply shortages.

1. Deferral of the Poisons Standard amendment implementation date

The proposed date of effect is stated as **1 October 2019**. This proposed timeframe provides insufficient time for sponsors of modified release paracetamol medicines to ensure packs are:

- re-designed;
- labelling, Product Information (PI) and Consumer Medicine Information (CMI) are prepared and TGA approved; and
- new product components are ordered, manufactured and distributed such that finished products are available for dispensing on the proposed date.

1.1 Timeframe for transition not consistent with the regulatory changes involved

Modified release paracetamol is one of the largest OTC medicinal products in Australian pharmacy calculated by dose unit volume. This equates to approximately 12 million packs (1.2 billion tablets) per annum across more than 5,500 pharmacies.[*] It would not be feasible to carry out all of the regulatory, manufacturing, transportation and distribution steps required to deliver the necessary amount of stock into sponsors' warehouses, wholesaler warehouses, or the pharmacy dispensary in only the 2-3 months allotted by the proposed effective Poisons Standard amendment date (if it is confirmed in the delegate's final decision).

It is a requirement of Schedule 3 that products have a TGA approved PI and CMI. Sponsors of modified release paracetamol products will need time to develop these

[*] Source: AC Nielsen pharmacy scan data MAT 10/3/2019

documents and then prepare a C3 variation application (in accordance with the Australian Regulatory Guidelines for OTC Medicines)[†] in the case of products that do not already have an approved PI and CMI. This is an important consideration given that the 44 product entries for modified release paracetamol products present on the ARTG are from eight different sponsors.

To the best of our knowledge few Schedule 2 medicines containing modified-release paracetamol have existing approved PIs and CMIs, as these are not a requirement of Schedule 2 medicines. Each sponsor would need to write its own PI document because the formulations of the available modified release paracetamol products, and the manner in which their bioequivalence has been measured, are not necessarily the same.[‡] For example, the innovator brand ([redacted]) was registered on the basis of it being bioequivalent to immediate release paracetamol while the generic modified release paracetamol products have been registered based on their bioequivalence to the innovator. The different formulations, and the clinical data available to support their use, will require documentation in each approved PI.

Notwithstanding the time and resource impact of preparing and submitting these documents, the TGA target evaluation times for such C3 applications are approximately 9 months (assuming two requests for information, and the product sponsor's response time being minimal).[§]

It is therefore not possible to have these documents written, reviewed and appropriately approved within the current timeframe set out in the delegate's interim decision.

1.2 Comparable TGA OTC medicine transition times for safety related label changes

Australian labelling requirements for non-prescription medicines (Therapeutic Goods Orders 69 and 92) require over-the-counter and complementary medicine labels to contain particular warning statements ('advisory statements') about specific risks related to use of the medicines. These advisory statements are set out in the TGA document 'Required Advisory Statements for Medicine Labels' (RASML). Such labelling changes which affect packaging text (which are not dissimilar in complexity to those required by the move of modified release paracetamol from S2 to S3) normally afford a transition period of 18 months from the date of TGA publication before they come into effect.[**] The purpose of such a transition period is designed to acknowledge the complexities of medicines supply chains that need to account for: artwork already produced, and existing

[†] Source: https://www.tga.gov.au/book-page/change-table-product-information-pi

[‡] Source: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2014-11

[§] Source: https://www.tga.gov.au/target-evaluation-times-otc-medicine-applications

[**] Source: (https://www.tga.gov.au/publication/required-advisory-statements-medicine-labels-rasml).

stock at all points in the supply chain – in transit, in sponsor warehouse(s), at wholesalers, and at pharmacies.

1.3 Comparable rescheduling decision precedents for consideration

In this regard, we draw on prior precedents from previous up-schedules. There have only been a few comparable up-schedules to draw on, both relate to analgesics in combination with codeine. These are relevant as they were both decided on the basis of improving patient safety, not unlike the present interim decision.

1.3.1 NDPSC Record of Reasons of Meeting 56 – June 2009

During the consideration of the rescheduling of combination analgesics containing codeine from Schedule 2 to Schedule 3 the Members of the NDPSC agreed that a deferred implementation was justified and applied an 11-month implementation from the date of the meeting (i.e. May 2010). It was deemed that this timing would be more appropriate, enabling simultaneous change with the date of implementation of Amendment 3 to SUSDP 24.[††] The deferral was in recognition of the substantial regulatory impact from the decision.

1.3.2 TGA Delegate's Final Decision resulting from ACMS #15 and #17 - Codeine containing medicines

In this decision the delegate noted the critical importance of implementation timeframes in enabling businesses to reposition themselves with this decision without being at odds with the protection of public health and safety. The delegate was informed that the minimum timeframe to comply with an up-scheduling decision appears to be 9 to 12 months.[‡‡]

The Delegate's final decision on the rescheduling of codeine containing medicines from Schedules 2 and 3 to Schedule 4 was published on 25 January 2017.[§§] By applying an implementation date of 1 February 2018, that decision provided a deferred implementation of over 12 months from the date of the delegate's final decision, which is consistent with the timeframe being sought by GSKCH in the instance of the rescheduling of modified release paracetamol.

[††] Source: https://www.tga.gov.au/sites/default/files/ndpsc-record-56.pdf

[‡‡] Source: https://www.tga.gov.au/sites/default/files/scheduling-delegates-final-decision-codeine-december-2016.pdf

[§§] Source: https://www.tga.gov.au/book-page/summary-delegates-final-decisions-7

GSKCH Recommendation 1: GSKCH proposes that a longer transitional timeframe be established, with an amendment to the Poisons Standard being made effective no earlier than 1 June 2020. Ideally later, to give industry time to transition what is one of the biggest products by dose unit volume in pharmacy, given similar precedents suggest 11-12 months.

2. Labelling exemption provisions needed for manufactured stock for supply in the states and territories

In addition, to the Poisons Standard amendment effective date deferral, sponsors will need labelling exemptions from each of the state and territory health authorities given that they have compliance jurisdiction via their respective Poisons schedules.

Otherwise sponsors, wholesalers and pharmacies will find themselves in a position whereby they cannot reasonably supply existing Schedule 2 labelled product without a workable labelling exemption. Indeed many sponsors may find themselves in the situation whereby stock destruction is the only viable means to achieve regulatory compliance. It is neither feasible, reasonable, nor cost effective to expect that sponsors can over-sticker existing stock in the supply chain when that stock can run into the many millions of packs sourced from a lengthy and complex supply chain and involve product that has a shelf life of up to 48 months.[***] It is not unreasonable to expect that all these added compliance costs would need to be passed on to the end consumer.

We would argue that this is not the best use of what would be otherwise useable and saleable product, and that such impact should be taken into account when millions of elderly patients are dependent on cost effective and timely access to modified release paracetamol as the foundation of their OA pain management regimen.

Given the high volume of tablets involved (see above), omission of the provision of an overarching labelling exemption by the states and territories would have significant impact on access to modified release paracetamol. This would have further impact on consumers, with a net negative impact on patient outcomes. Moreover, public submissions from the RACGP, Arthritis Australia, and Pain Australia raised concerns that an up-scheduling may have unintended consequences on medication cost and access for patients using modified release paracetamol for the management of chronic pain. It is therefore pertinent to ensure uninterrupted access to modified release paracetamol by avoiding the premature imposition of a regulatory burden that may restrict supply or impose an unintended medicines shortage.

[***] [redacted] ARTG Entry. Available from: https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs%2FPublicHTML%2FpdfStore.nsf&docid=4114AE452448CBBACA258385003CAE2B&agid=(PrintDetailsPublic)&actionid=1

As was the case with the longer transition timeline afforded for the two rescheduling events surrounding codeine containing medicines from S2 to S3 (2009) and S2/S3 to S4 (2017) respectively, similarly the states and territories afforded existing quantities of such labelling present in the supply chain sufficient time to be exhausted by sponsors, wholesalers and pharmacies.

GSKCH recall that 10-12 months labelling exemption was afforded in those previous rescheduling instances, and so given the importance of modified release paracetamol to elderly patients and the significant volume of stock involved that a labelling exemption period of 12 months from the date the Poisons Standard is amended also be afforded in this instance.

Based on this previous experience we would also request that a single body (e.g. CHP Australia) be permitted to request the labelling exemption from one state medicines regulator (e.g. NSW) on behalf of all sponsors. Thereafter, that this labelling exemption be forwarded to the other state and territory medicines regulators for their information and processing of a like labelling exemption for the same period. This would provide the most efficient and timely means to address this need given the number of products and sponsors involved.

GSKCH Recommendation 2: GSKCH proposes that a co-ordinated approach be adopted by the states and territories whereby an overarching labelling exemption be granted to all sponsors, wholesalers and pharmacies so they may supply modified release paracetamol when labelled and packed as a Schedule 2 medicine from 1 June 2020, when such preparations are rescheduled to Schedule 3, until 31 May 2021, or until existing Schedule 2 stock is exhausted, whichever is the earlier.

3. Communication of important changes in medicine access

The proposed timeframe provides no workable time within which to communicate this important change in medicine availability to consumers and to healthcare professionals.

Pharmacists and their assistants, in particular, will need to be educated as to how to inform customers (who are long accustomed to self-selecting modified release paracetamol) about their options for continued use of this medicine for the relief of pain associated with osteoarthritis.

Prior experience with modified release paracetamol dictates the need for sufficient time to be allocated for consumer education regarding availability. For example, as a result of the January 2016 decision to remove modified release paracetamol 665mg from the Pharmaceutical Benefits Scheme there was significant consumer concern and confusion that resulted in unpredictable buying patterns, which in turn resulted in supply shortages.

The need for clear communication to consumers to ensure there is no confusion over current and future access to modified release paracetamol has been raised in several of the public comments. Ideally such communications should begin to take place several months prior to the change in scheduling. Importantly these communications will need to utilise updated packaging, further underpinning the need for a deferral of the

implementation date of the amendment to the Poisons Standard to come into effect from no sooner than 1 June 2020.

Whilst GSKCH (as a member of CHP Australia) is committed to undertaking broad stakeholder engagement to communicate the change, we are just one of eight sponsors impacted, and a significant number of those are not members of CHP Australia, and are not bound by its decisions.

GSKCH Recommendation 3: GSKCH proposes that a co-ordinated approach be adopted by TGA with all stakeholders, to effectively communicate the rescheduling so that healthcare professionals and consumers are well prepared for the change in labelling and OTC access. A deferred implementation date for the rescheduling to take effect will allow sufficient time for an effective communication programme.

4. Conclusion

The desired outcome of the current consultation has been to ensure continued access to modified release paracetamol for the relief of osteoarthritis pain while mitigating potential risks.

In principle, GSKCH does not agree with the proposed rescheduling of modified release paracetamol from Schedule 2 to Schedule 3. However, GSKCH does not challenge the interim decision, except to request that the time period of implementation be deferred with a minimum implementation date of 1 June 2020, and ideally longer. Further that the state and territory medicines regulators confer a 12-month labelling exemption from the deferred Schedule 3 effective date for product labelled as a Schedule 2 medicine. This will help to ensure feasible industry compliance and enable adequate time for consumer education and to ensure pharmacists, and their staff, are provided with the tools, information and ongoing product availability needed to ensure that patients' needs continue to be managed appropriately post the scheduling change.

Yours sincerely,

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