Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Notice of interim decisions to amend (or not amend) the current Poisons Standard

3 February 2023

TGA Health Safety Regulation

Confidentiality
All submissions received will be placed on the TGA's Internet site, unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked "IN CONFIDENCE". Reasons for a claim to confidentiality must be included in the space provided on the TGA submission form. For submission made by individuals, all personal details, other than your name, will be removed from your submission before it is published on the TGA's Internet site. In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission form.

Contents

1. Notice of interim decisions made under Regulation 42ZCZN of the *Therapeutic Goods Regulations 1990*

This web publication constitutes a notice for the purposes of regulation 42ZCZP of the *Therapeutic Goods Regulations 1990* (the **Regulations**). In accordance with regulation 42ZCZP, this notice sets out:

- the interim decisions made by a delegate of the Secretary of the Department of the Health and Aged Care (the **Delegate**) under regulation 42ZCZN in relation to proposed amendments to the current Poisons Standard which were referred to an expert advisory committee[1] under subdivision 3D.2 of the Regulations in November 2022;
- the proposed date of effect of the proposed amendments (in circumstances where the interim decision proposes an amendment to the current Poisons Standard).

In accordance with regulation 42ZCZP, interested persons (including the applicant requesting the amendment) are invited to make submissions to the Secretary in relation to these interim decisions on or before **3 March 2023**.

There are two consultations hubs relating to this notice:

- Submissions relating to the decisions regarding **paracetamol** should be provided through the consultation hub for paracetamol; and
- Submissions relating to **any other substance in the notice** should be provided through the second consultation hub.

Submissions will be considered by the Delegate in making the final decision.

Please note that in accordance with subregulation 42ZCZQ(4) of the Regulations, the Secretary must publish all relevant submissions received, unless the Secretary considers the information to be confidential information.

Defined terms

In this notice the following defined terms are used in addition to those above:

- the *Therapeutic Goods Act 1989* (Cth) (the **Act**)
- the Scheduling Policy Framework 2018 (the **SPF**);
- the Scheduling handbook: Guidance for amending the Poisons Standard (the **Handbook**); and
- the Therapeutic Goods Administration (the **TGA**).

Note: additional terms are also be defined for individual decisions.

[1] Established under sections 52B and 52C of the *Therapeutic Goods Act 1989* (Cth).

2. Interim decisions on proposed amendments referred to the Advisory Committee on Medicines Scheduling (ACMS #40, November 2022)

2.1 Interim decision in relation to paracetamol

Introduction

The TGA sought public comment on whether the current scheduling of paracetamol is appropriate, considering the available data on paracetamol poisoning which included intentional overdose, associated hospitalisations and deaths. Comment was specifically sought on a variety of options that the Delegate proposed for amending the Poisons Standard in relation to paracetamol. These were proposed in view of the findings and recommendations in the independent expert report on intentional paracetamol self-poisoning that was commissioned by the TGA.

The proposed changes included the following:

- ***Requirement for blister packs.*** It is slower to consume paracetamol tablets or capsules that must be individually ejected from blister or strip packs as compared to other packaging (e.g. bottles). Slowing the consumption of multiple tablets or capsules by restricting these dosage forms to being presented in blister or strip packs may reduce the likelihood of overdose and harm from impulsive attempts to self-poison.
- ***Pack size restrictions.*** For example, maximum pack sizes for unscheduled products reduced from 20 to 12 or 16 tabs; S2 pack sizes reduced from 100 to 24 or 32. This would reduce the number of grams of paracetamol held in homes and thus the numbers of very large overdoses taken in impulsive self-poisonings.
- ***Pack number limits.*** Most (~95%) sales of paracetamol tablets involve the purchase of 1 or 2 packs. Making this the maximum number of packs that can be purchased in one transaction would reduce home stockpiles, and likely also reduce the number of very large overdoses, which have much higher morbidity and risk of death.
- ***Sale from behind the counter.*** The prohibition of display and self-selection of paracetamol in general (non-pharmacy) retail outlets may discourage impulsive purchasing by those vulnerable to overdosing with paracetamol.
- ***Modified Release paracetamol restrictions.*** This product is designed for long-term use (e.g., for osteoarthritis), rather than for acute pain. Prescription only (S4) scheduling would be expected to reduce inappropriate use of this product which is harder to treat in overdose than immediate release paracetamol.
- ***Age restrictions.*** An 18+ age restriction on the purchasing of over-the-counter analgesics would be expected to reduce poisonings among 10–17-year-olds.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard as follows:[2]

Schedule 4

PARACETAMOL:

a) when combined with aspirin or salicylamide or any derivative of these substances **except** when separately specified in these Schedules; or

b) when combined with ibuprofen in a primary pack containing more than 30 dosage units; or

c) in modified release tablets or capsules containing more than 665 mg paracetamol; or

d) in non-modified release tablets or capsules containing more than 500 mg paracetamol; or

e) in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol; or

f) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules **except** in ~~Schedule 2 or~~ Schedule 3; or

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~~3; or

h) for injection; or

i) for the treatment of animals.

Schedule 3

PARACETAMOL:

a) when combined with ibuprofen in a primary pack containing 30 dosage units or less **except** when included in Schedule 2; or

b) in modified release tablets or capsules containing 665 mg or less paracetamol enclosed in a primary pack containing not more than 100 tablets or capsules; or

c) in modified release-tablets or capsules containing 665 mg or less paracetamol enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

d) in non-modified release tablets or capsules containing not more than 500 mg paracetamol and in a primary pack containing not more than 100 tablets or capsules **except** when included in or expressly excluded from Schedule 2; or

[2] Proposed additions are shown in green underlined font, proposed deletions are shown in red strikethrough font, and text without this formatting represents the current text in the Poisons Standard.

e) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

f) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules **except** when included in or expressly excluded from Schedule 2; or

g) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

h) in liquid preparations for oral use **except** when in Schedule 2.

Schedule 2

PARACETAMOL for therapeutic use:

a) in liquid preparations for oral use containing a maximum of 10 g of paracetamol per container; or

b) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than 12 dosage units per pack; or

c) in tablets or capsules in blister or strip packaging enclosed in a primary pack containing not more than 32 ~~100~~ tablets or capsules; or

~~d) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or~~

e) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 16 ~~50~~ wrapped powders or sachets of granules; or

~~f) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or~~

g) in other preparations **except**:

i) when included in Schedule 3 or 4; or

ii) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaifenesin or when combined with effervescent agents) when:

(A) enclosed in a primary pack that contains not more than 8 ~~10~~ such powders or sachets of granules,

(B) compliant with the requirements of the Required Advisory Statements for Medicine Labels,

(C) not labelled for the treatment of children 6 years or age or less, and

(D) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaifenesin; or

iii) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaifenesin or when combined with effervescent agents) when:

(A) packed in blister or strip packaging ~~or in a container with a child-resistant closure~~,

(B) in a primary pack containing not more than 16 ~~20~~ tablets or capsules,

(C) complaint with the requirements of the Required Advisory Statements for Medicine Labels,

(D) not labelled for the treatment of children 6 years of age or less, and

(E) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaifenesin.

Materials considered

In making this interim decision, the Delegate considered the following material:

- The delegate-initiated proposal to amend the current Poisons Standard with respect to paracetamol (the **Proposal**);
- The 190 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**);
- The advice received from the 40th meeting of the Advisory Committee on Medicines Scheduling (the **Committee**);
- The findings and recommendations in the independent expert report of the risks of intentional self-poisoning with paracetamol, published on the TGA website on 14 September 2022 (the **Report**);
- Subsection 52E(1) of the Act, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters considered necessary to protect public health;
- the SPF; and
- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that the scheduling of paracetamol be amended in the Poisons Standard substantially in line with my interim decision as follows:

Schedule 4

PARACETAMOL:

a) when combined with aspirin or salicylamide or any derivative of these substances **except** when separately specified in these Schedules; or

b) when combined with ibuprofen in a primary pack containing more than 30 dosage units; or

c) in modified release tablets or capsules containing more than 665 mg paracetamol; or

d) in non-modified release tablets or capsules containing more than 500 mg paracetamol; or

e) in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol; or

f) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules **except** in ~~Schedule 2 or~~ Schedule 3; or

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~~3; or

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PARACETAMOL:

a) when combined with ibuprofen in a primary pack containing 30 dosage units or less **except** when included in Schedule 2; or

b) in modified release tablets or capsules containing 665 mg or less paracetamol enclosed in a primary pack containing not more than 100 tablets or capsules; or

c) in modified release-tablets or capsules containing 665 mg or less paracetamol enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

d) in non-modified release tablets or capsules containing not more than 500 mg paracetamol and in a primary pack containing not more than 100 tablets or capsules; or

e) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 16 wrapped powders or sachets of granules; or

f) in liquid preparations for oral use **except** when in Schedule 2.

Schedule 2

PARACETAMOL for therapeutic use:

a) in liquid preparations for oral use containing a maximum of 10 g of paracetamol per container; or

b) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than 12 dosage units per pack; or

c) in tablets or capsules in blister or strip packaging enclosed in a primary pack containing not more than 32 ~~100~~ tablets or capsules; or

d) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

e) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 16 ~~50~~ wrapped powders or sachets of granules; or

f) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

g) in other preparations **except**:

i) when included in Schedule 3 or 4; or

ii) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaifenesin or when combined with effervescent agents) when:

(A) enclosed in a primary pack that contains not more than 8 ~~10~~ such powders or sachets of granules,

(B) compliant with the requirements of the Required Advisory Statements for Medicine Labels,

(C) not labelled for the treatment of children 6 years or age or less, and

(D) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaifenesin; or

iii) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaifenesin or when combined with effervescent agents) when:

(A) packed in blister or strip packaging ~~or in a container with a child-resistant closure~~,

(B) in a primary pack containing not more than 16 ~~20~~ tablets or capsules,

(C) complaint with the requirements of the Required Advisory Statements for Medicine Labels,

(D) not labelled for the treatment of children 6 years of age or less, and

(E) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaifenesin.

My interim decision varies from the recommendation of the Committee in regard to the scheduling of bulk medicine packs. No advice was provided by the Committee on bulk medicine packs but I have decided to amend the scheduling of these to align with other amendments as set out in my interim decision.

The Committee recommended consultation with relevant stakeholders regarding a possible implementation date.

Members agreed that the relevant matters under Section 52E(1) of the Act included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters considered necessary to protect public health.

The reasons for the advice included:

a) *the risks and benefits of the use of a substance*

Risks:

- The size of packs that are currently available mean many households have surplus supply.
- Modified release formulations pose additional challenges in poisoning events.
- Some people, particularly younger people, at risk of harm from intentional overdose.

Benefits:

- Low cost.
- Usually well tolerated with minimal side effects or precautions/contraindications associated with use.

b) *the purposes for which a substance is to be used and the extent of use of a substance*

- Long history of use as an analgesic for many common pain ailments, including chronic pain.
- Widely available in supermarkets, convenience stores and pharmacies.

c) *the toxicity of a substance*

- Low toxicity when used in therapeutic doses, significant toxicity when 10 g or more is taken as a single dose for an average sized adult (including when taken as an intentional self-poisoning).
- Untreated overdose can result in acute liver failure and death.

d) *the dosage, formulation, labelling, packaging and presentation of a substance*

- Many formulations, pack sizes and presentations available at present.
- Evidence that adjustments to packaging (blister packs and reduces pack sizes) may reduce risk of intentional self-poisoning with paracetamol products.

e) *the potential for abuse of a substance*

- Low potential for abuse with regards to psychoactive effects, however there is considerable evidence of nonmedical use in the context of intentional poisoning.

f) *any other matters that the Secretary considers necessary to protect public health*

- Proportion of paracetamol used for intentional self-poisoning out of all paracetamol sold/supplied in Australia to ensure equity of access. However, consequences of intentional self-poisoning can be high morbidity (irreversible liver damage) and even death.
- Pack size ingested in cases of deliberate self-harm are reflective of the pack sizes that are currently available for sale. Smaller pack sizes available for spontaneous purchase should be less than the toxic dose.
- 10% of cases of deliberate self-harm/overdose involved going out to purchase paracetamol, however over all the source of paracetamol was unknown in a large proportion of cases.
- Changing current access controls may have unintended impacts on legitimate use of paracetamol e.g., imposing restrictions that are too severe could result in substitution with other medications as it may be perceived that paracetamol is unsafe/harmful.

Reasons for the interim decision (including findings on material questions of fact)

I have made an interim decision to amend the scheduling of paracetamol in the current Poisons Standard to reduce pack sizes and mandate blister packs in the manner detailed above.

Between 14 September and 14 October 2022, I sought public submissions on a variety of options for amending the Poisons Standard that I raised as delegate-initiated proposals to address the risks of intentional paracetamol overdose. My interim decision adopts two of the options with modification.

In providing my reasons for adopting these options, I will first set out the broad benefits and risks of paracetamol that were central to my consideration of all the options, along with other cross-cutting factors according to the criteria I am required to consider under section 52E of the Act. I will then present my reasoning for reaching the view that reducing pack sizes and mandating blister packs, as set out in my decision, strike a proportionate approach to minimising the harm from paracetamol overdose, balanced against providing appropriate access to paracetamol for pain relief. Finally, I will provide my reasons for not adopting options related to pack number limits, sales from behind the counter, further modified release (MR) restrictions, and age restrictions, in relation to which I have decided to not amend the Poisons Standard.

Matters considered in accordance with section 52E of the Act including the benefits and risks of paracetamol

I agree with the Committee's findings on the relevant provisions of section 52E of the Act.

In making my decision, I have weighed the benefits of paracetamol use against its toxicity and risks from abuse, in accordance with paragraphs 52E(1)(a) and (c) of the Act. Central to my decision is the challenge of balancing appropriate access to paracetamol given its benefits as an effective and widely used analgesic on the one hand, with the significant risk of morbidity and mortality from its intentional misuse and a need for effective self-poisoning harm minimisation on the other.

I recognise that paracetamol has a well-established safety profile at therapeutic doses, which has contributed heavily to its widespread use for acute and chronic pain and to reduce fever. Paracetamol is well tolerated with a favourable drug and disease interaction profile.[3] It remains the preferred option for many Australians as it can be used concomitantly with common medications and in numerous conditions such as cardiovascular, gastrointestinal, respiratory, and renal diseases.[4] I acknowledge that the introduction or tightening of any restrictions on access to paracetamol through scheduling has the potential to impact upon the significant benefits of paracetamol for individuals and public health.

However, the amendment to the scheduling of paracetamol was proposed because of the findings detailed in the Report concerning the significant risks of acute paracetamol toxicity and its potential to cause liver failure and death in severe overdoses. There has been a concerning increase in the rates of intentional overdose, particularly among adolescent females with paracetamol taken in around 50% of cases.[5] I note the nature of intentional paracetamol overdose is impulsive and mostly involves the consumption of paracetamol already in the home.[6] In relation to paragraphs 52E(1)(c) and (d) of the Act, the Report shows that severe paracetamol overdoses of 25 g or higher disproportionately cause severe liver toxicity.[7] Concerningly, this threshold is less than 10 times the recommended maximum daily dose of paracetamol. On this basis, and in consideration of all the Submissions received, I consider that restrictions on access to paracetamol must be tightened to address the increasing incidence of Australians intentionally overdosing with paracetamol, and that this is appropriately achieved through amendment of the Poisons Standard.

The public submissions, which span peak bodies representing consumers, healthcare practitioners and industry, and individuals, expressed a broad spectrum—and in some cases strongly divergent—views about which or indeed any options should be implemented. This underscores why I have sought in making my interim decision to strike an appropriate balance between minimising severe paracetamol overdoses and maintaining appropriate access to paracetamol, constraints to which pose new and unintended risks that I will outline below.

I acknowledge that the introduction or tightening of any restrictions on access to paracetamol through scheduling has the potential to impact upon the significant benefits of paracetamol for individuals and public health as explained above. Although appropriate access to paracetamol as a safe and effective option in pain and febrile conditions is essential, I consider that some change to access to paracetamol under the Poisons Standard is required and justified as part of a broader strategy to reduce the relatively small but devastating consequences of severe paracetamol overdoses.

[3] https://www.mimsonline.com.au/Search

[4] https://amhonline.amh.net.au

[5] the Report p.69

[6] the Report p.55

[7] the Report p.123

In turning my mind to the Handbook and paragraph 52E(1)(d) of the Act, and noting the concerns raised by the Pharmacy Guild of Australia, the current risks of paracetamol outlined above do not align with the 'reasonable safety' guidelines of unscheduled medicines for which warning labels should sufficiently mitigate the risk of inappropriate use. The Report highlighted that warning labels are unlikely to be an ineffective deterrent for intentional paracetamol overdoses. Therefore, although amendments to warning labels would pose a low implementation burden, the evidence suggests that they are not efficacious in reducing severe intentional overdoses.

Cutting across all options that I considered in making this interim decision were that any restriction should reduce the amount of paracetamol available within the home, thereby reducing the likelihood that impulsive self-poisoning leads to severe toxicity. Specifically, the Report highlights that:

- over half the time people are taking what is readily available in the home, particularly young people, as they don't have access to other medications, such as prescription drugs.[8]
- the most ingested pack size was 96/100 tablets.[9]
- the majority of people who intentionally overdosed had suicidal intent and did so impulsively.[10]
- overdosing over 25 grams disproportionately causes significant harm. It was noted that overdoses of 25 grams or lower are easier to treat.[11]

The Committee acknowledged these key matters and advised that a focus on impulsiveness, paracetamol in the home, and severity of overdose is required when considering the potential options.

I note the following concerns raised in the Submissions regarding reduced access and unintentional consequences. The concerns regarding access were increased costs, impacts on chronic pain management, timely access, and the particular impacts on certain population groups, such as those in rural and remote areas, those with hand dexterity and mobility issues, and those under the age of 18 living independently. The concerns regarding unintentional consequences were inadvertent increases in stock-piling in response to restrictions, resorting to inappropriate use of anti-inflammatories, and damaging the public's perception of paracetamol as being safe for use in accordance with instructions. I have considered these concerns in making my decision and I will address them throughout my reasoning. I also acknowledge concerns, particularly of Consumer Health Products (CHP) Australia, around the limitations of the available data relied upon in the Report and the dissimilarity of the Australian and international regulatory systems. However, I am satisfied the data considered and the findings in the Report are sufficient to warrant my decision.

Reasons for tightening pack size restrictions and mandating blister packaging

As outlined above, I have made the interim decision to implement amendments to the pack size restrictions and blister packaging requirements of paracetamol preparations available for general sale (unscheduled) and pharmacy (Schedule 2 and 3) sale. This is in substantial agreement with the advice received from the Committee, and I am of the view that these two

[8] the Report p. 4 and 69

[9] the Report p. 69

[10] the Report p. 75

[11] the Report p. 123

options are warranted and sufficient, at the core of which is my satisfaction that they strike an appropriate balance between the benefits and risks of paracetamol.

In coming to this decision, I refer to three findings of the Report: (1) the disproportionate effects of severe overdoses involving 25 g or higher of paracetamol,[12] (2) that over half of intentional paracetamol overdoses involved the consumption of the entirety of whatever packs were available,[13] and (3) that paracetamol overdoses are frequently impulsive using product already present in the home.[14] I consider that the combination of both options is likely to sufficiently address these aspects so as to significantly minimise harm, while having a minimal impact on access to paracetamol for therapeutic use.

Pack sizes. A reduction in pack sizes is likely to reduce the total quantity of paracetamol available in the home, and thus available to be impulsively consumed. Pack sizes of 500 mg tablets or capsules up to 50 g total paracetamol content that are available over-the-counter in Schedule 2 are frequently involved in intentional overdose and exceed 25 g that can cause severe liver injury. I consider that it is necessary to reduce the maximum size of Schedule 2 packs to 32 tablets or capsules containing 500 mg paracetamol, and make corresponding changes to wrapped powders or sachets of granules, to a total paracetamol content well below an amount likely to produce severe liver injury.

Additionally, data from the Report show that a pack size reduction down to 16 tablets or capsules of 500 mg paracetamol in general retail is expected to contribute to reducing the amount of paracetamol consumed in an overdose[15] to below minimum toxic dose of 10 g.[16]

I concur with the Committee that quantities of 32 and 16 tablets or capsules of 500 mg paracetamol appropriately provide a 4 day supply as pharmacy only (Schedule 2) and a 2 day supply by general retail, respectively, that will reduce harm from self-poisoning without unreasonably impairing access for therapeutic use. I note this is supported by the Report's findings where pack sizes were shown to reduce deaths from poisonings by a third.[17]

I acknowledge the concern raised by Painaustralia that pack size restrictions will disproportionately burden those suffering from chronic pain who rely on larger pack sizes currently available in pharmacies. A similar concern was also raised for consumers living in rural and remote areas for whom access to General Practitioners may be challenging. However, I wish to emphasise that my interim decision proposes to move large pack sizes (up to 100 tablets or capsules) from Schedule 2 to Schedule 3 rather than Schedule 4 of the Poisons Standard, as put forward in the Proposal. I agree with the Committee that these amendments to pack size restrictions in my interim decision will maintain appropriate access to quantities required for the management of acute and chronic pain. For the purposes of paragraph 52E(2)(a) of the Act, it is also consistent with the scheduling factors for a Schedule 3 medicine.[18] I am satisfied that my decision to place larger pack sizes in Schedule 3 will ensure that those suffering from chronic

[12] the Report p. 123

[13] the Report p. 80

[14] the Report p. 106

[15] Donohoe, E., Walsh, N., & Tracey, J. A. (2006). Pack-size legislation reduces severity of paracetamol overdoses in Ireland. Ir. J Med Sci, 175(3), 40-42.

[16] the Report pp 17-18.

[17] the Report p. 4

[18] Factor 2 (The use of the medicine is not expected to produce dependency at either the established therapeutic dose or at supratherapeutic doses. Where risk of misuse, abuse or illicit use is identified, the risk can be minimised through pharmacist-consumer consultation) and factor 4 (Where the medicine is intended for recurrent or subsequent treatment of a chronic condition, pharmacist intervention is required to monitor safe use of the medicine following recommendation by a medical practitioner or other authorised prescriber).

pain can continue to have access to larger packs of paracetamol from a pharmacy under pharmacist supervision and avoid the cost of purchasing multiple packets through general sale. Moreover, I am satisfied that there is sufficient access to pharmacies in rural and remote areas to access packs sizes of up to 100 tablets or capsules, and otherwise that states and territories can permit packs of 32 tablets or capsules as Schedule 2 medicines to be supplied in general retail outlets in rural and remote settings where there are no nearby pharmacies.

Blister packs. I refer to data in the Report that found blister pack preparations were associated with lower overall consumption of paracetamol compared to loose packs in an intentional overdose.[19] Blister packaging is likely to interrupt the impulsive intentional paracetamol overdoses as the process of isolating the tablets or capsules for ingestion would be arduous and time consuming. It is likely to have a disproportionately greater effect on large overdoses, resulting in fewer capsules or tablets being consumed and reducing the incidence of the most devastating consequences, namely liver failure and death.

I acknowledge but am not persuaded by the submission from one industry body emphasising the minimal impact of blister pack mandates given half of people consume all available tablets during an intentional paracetamol overdose.

I also acknowledge concerns raised by the Australian Pain Management Association and ChronicPain Australia in their submission, and the joint position statement from the Accessible Product Design Alliance,[20] highlighting the struggle of consumers with inaccessible products. While blister packs are minimally restrictive for many, they have the potential to restrict those with hand dexterity and mobility issues. I agree with Arthritis Australia that manufacturers should apply accessible design principles and user testing to their products. However, I am satisfied that under pharmacist supervision larger quantities of paracetamol without blister packaging under my proposed amendments to Schedule 3 of the Poisons Standard ensures supply to consumers without considerable inconvenience.

Review of Submissions for the two options. I am of the view that my interim decision accords with the options for amending the Poisons Standard for which there was the broadest support expressed in the Submissions. I have considered all 190 responses received during the pre-meeting consultation and note that over 70% of respondents supported some level of blister packing mandates, while just over 30% of respondents supported some form of pack size reductions. I am satisfied that the modifications to up-schedule larger pack sizes to Schedule 3 instead of Schedule 4, thereby maintaining convenient pharmacy access, addresses a key concern expressed in many of the Submissions.

I acknowledge the concerns of industry and the cost and operational impacts of blister pack mandates and changes to pack sizes. I am reassured by the partial support provided by CHP Australia and GlaxoSmithKline Consumer. Despite the impact to industry, I am of the opinion that this is the best available option in striking a balance between the benefits and risks of paracetamol, in a context where there must be some change to the scheduling of paracetamol.

Overall, I note that most peak bodies and consumer submissions were in support of pack size reductions and blister pack mandates. I have formed the view that the combination of these two options address my key concerns without disproportionately compromising access for therapeutic use. I consider this in conjunction with the opportunity to minimise harm through

[19] Hawton, K., Ware, C., Mistry, H., Hewitt, J., Kingsbury, S., Roberts, D., & Weitzel, H. (1996). Paracetamol self-poisoning: Characteristics, prevention and harm reduction. British Journal of Psychiatry, 168(JAN.), 43-48. DOI: http://dx.doi.org/10.1192/bjp.168.1.43

[20] https://arthritisaustralia.com.au/accessible-design-division/accessible-product-design-alliance/accessible-product-design-alliance-position-statement/

public health initiatives that promote the safer storage of medicines, particularly for vulnerable adolescents.

Considerations and exclusion of proposed options

Having decided to reduce pack sizes and mandate blister packs, and I am satisfied that it is neither necessary nor appropriate to implement at this time any of the remaining options on which I sought public consultation. In particular, I am not persuaded on the currently available evidence that the additional options would strike an appropriate balance between the risks and benefits of consumer access to paracetamol as set out earlier in my reasons.

Age Restrictions. It was highlighted in the Report that, although data on age restrictions have shown their effectiveness internationally,[21] such restrictions are expected to be limited in Australia. This is because data from the Report showed that most paracetamol ingested in self-poisoning was found to be readily available in the home, and that measures such as smaller pack sizes already exist overseas. The Report found that only a small proportion of those who overdosed reported that they had recently purchased the paracetamol ingested,[22] and a large proportion of intentional overdoses, notably among adolescents, were not planned.[23] Therefore, age restrictions at the point of sale are likely to have a limited impact on impulsive intentional overdosing behaviour in the most vulnerable age group, or reduce the amount of paracetamol available in the home. For the same reasons it is also unlikely to reduce the number of severe cases. I agree with the issues highlighted by Global Healthy Living Foundation Australia and other submissions that such a change would disproportionately and unjustifiably affect access for those living independently under the age of 18.

Behind the counter in general retail. The prohibition of display and self-selection of paracetamol in general retail outlets has also been excluded from my interim decision. I have taken into account section 52E(1)(f) of the Act and I share the concerns of the Committee and other peak bodies that sales from behind the counter would undermine patient confidence in the overall safety of paracetamol if it adopts similar measures to products like cigarettes. In addition, I consider it essential that consumers are provided the opportunity to read the product packaging without impediment, and compare against other substances, such as analgesics. I believe that this option would not sufficiently address my key concerns and would cause disproportionate detriment to the management of pain in the community and inconvenience to consumers. I also note concerns raised by the Australian Retailers Association regarding the substantial cost, logistical challenges and staff training associated with this proposed change.

Reflecting on paragraphs 52E(1)(a) and (f) of the Act, I acknowledge concerns raised by the Royal Australian College of General Practitioners (RACGP) and other peak bodies that restrictions to paracetamol will result in increased use of other unscheduled and over-the-counter substances, both for acute and chronic pain, and to reduce fever, or intentional overdose. Most concerns lie in patients resorting to NSAIDs for therapeutic use and the consequent longer term chronic toxicity of NSAIDs (much less favourable over the longer term compared to paracetamol). This contrasts with intentional overdose, for which current evidence does not suggest that paracetamol restrictions result in the substitution of other substances for

[21] Morthorst, B. R., Erlangsen, A., Chaine, M., Eriksson, F., Hawton, K., Dalhoff, K., & Nordentoft, M. (2020). Restriction of non-opioid analgesics sold over-the-counter in Denmark: A national study of impact on poisonings. Journal of Affective Disorders, 268, 61-68. doi:http://dx.doi.org/10.1016/j.jad.2020.02.043et al., 2020)

[22] the Report p.55

[23] the Report p. 55 and 82

use in intentional overdose.[24] In addition, ibuprofen, the most readily substituted alternative, is less toxic in acute overdoses.[25]

Pack limits. While restrictions on the number of packs that can be purchased in a single transaction are likely to be an effective strategy in reducing intentional overdoses, I am of the opinion that the benefits of this option can be better achieved through pack size reductions. When reflecting on the practicality of this option, I acknowledge there are considerable challenges with enforcing limits on packs per sale. I also note that Professional Practice Guidelines for pharmacists already recommends supply of 1 pack only per transaction for Schedule 2 and 3 medicines unless there are extenuating circumstances. [26] In addition, the Report demonstrated that 95% of sales currently involve the purchase of only 1 or 2 packs. Additionally, I am aware that some supermarkets voluntarily enforce pack number limits per transaction across their analgesic product range, which includes paracetamol. I note the submission from CHP Australia that highlights the current initiatives to support supermarket retailers in implementing a two-pack limit on paracetamol. I commend this initiative and strongly encourage retailers to restrict sales to a single pack at a time. In relation to paragraph 52E(1)(f), I have considered Painaustralia's comments regarding the prevalence of pain of those living rurally or remotely and the additional impacts of pack number restrictions on those with already reduced access. These concerns support my conclusion that pack size reductions are a more appropriate measure.

Modified release restrictions. I have considered MR preparations and their role in complicating overdoses,[27] but I have come to the conclusion that further restrictions on these preparations are premature and may disproportionately compromise the management of chronic pain.

I acknowledge RACGP's concerns regarding MR paracetamol self-poisonings and its association with poorer outcomes. However, I note the considerable concerns raised regarding the impacts this would have on the consumers ability to self-manage chronic pain, particularly regarding those living rural or remote areas. I agree with the Committee that insufficient time has lapsed since MR preparations were up-scheduled to Schedule 3 on 1 June 2020, especially considering its potential to disproportionately impact access in the context of chronic pain management.

I also agree with the Committee that the demographic of households using MR paracetamol, with the majority of osteoarthritis sufferers over the age of 55,[28] differs to the adolescent population group subject to concerning rises in overdoses.

Most peak bodies did not support this restriction and I make particular note of Painaustralia's concerns regarding the significant psychological effects of chronic pain sufferers regarding limitations on access to analgesics. At this point in time, I do not believe there is adequate evidence to support the further upscheduling of MR paracetamol on balance with the considerable burden to suffers of chronic pain, especially in the rural areas.

Concluding statements

Having considered the widespread use of paracetamol, the concerning rates of intentional overdose, and the current evidence available, I am of the view that my decision is balanced and a proportionate response to minimise harm from intentional self-poisoning with paracetamol. However, I acknowledge that if new evidence comes to light, particularly within an Australian

[24] the Report p. 126

[25] the Report p. 125

[26] Guidelines on practice-specific issues https://www.pharmacyboard.gov.au/codes-guidelines.aspx

[27] The Report p. 3

[28] https://www.aihw.gov.au/reports/chronic-musculoskeletal-conditions/osteoarthritis/contents/what-is-osteoarthritis

context, the scheduling of paracetamol could be reconsidered in future, particularly in relation to those options for change that I have not adopted in my interim decisions, to ensure an appropriate balance is maintained.

Considering the impacts of my decision, I recognise the need for a suitable transition period that does not unreasonably delay implementing measures to protect Australian consumers, yet provides sufficient time for industry to make any changes to the manufacturing of their products. I propose that the date of implementation be 1 June 2024.

Implementation date

1 June 2024

2.2 Interim decision in relation to ivermectin

Proposal

The applicant proposed deletion of the Appendix D entry relating to ivermectin (the **Proposal**). This would remove the current restrictions on the prescribing of ivermectin for unapproved indications by medical specialists in nominated fields. The restrictions were originally implemented due to concerns regarding the significant increase in off-label prescribing of ivermectin for the prevention and treatment of COVID-19.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to not amend the current Poisons Standard in relation to ivermectin.

Materials considered

In making this interim decision, the Delegate considered the following material:

- The application to amend the current Poisons Standard with respect to ivermectin (the **Application**);
- The 17 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**);
- The advice received from the 40th meeting of the Advisory Committee on Medicines Scheduling (the **Committee**);
- Subsection 52E(1) of the Act, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters considered necessary to protect public health;
- The SPF; and
- The Handbook

Summary of Committee advice to the Delegate

The Committee recommended that the current scheduling for ivermectin remains appropriate.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters considered necessary to protect public health.

The reasons for the advice included:

a) the risks and benefits of the use of a substance:

Risks

- Safety of higher doses used for prevention and treatment of COVID-19 is not well established.
- Evidence base for use in COVID-19 is not well established, in particular a lack of safety data to support use and for prolonged use.

Benefits

- Established benefits for treatment of parasitic and helminth infections.
- Benefit in relation to COVID-19 unlikely: No current recommendation for the use of ivermectin in COVID-19, due to a lack of evidence.

b) the purposes for which a substance is to be used and the extent of use of a substance:

- Ivermectin is a broad spectrum anti-parasitic agent.
- Registered indications include onchocerciasis, strongyloidiasis, crusted scabies in conjunction with topical therapy; human sarcoptic scabies when prior topical treatment has failed or is contraindicated.
- It is also used for rosacea (papulopustular), other intestinal nematode infections, cutaneous larva migrans and lymphatic filariasis.
- Not approved or recommended for prevention or treatment of COVID-19.

c) the toxicity of a substance:

- When used in high doses for the prevention or treatment of COVID-19, can result in severe adverse events such as severe skin reactions accompanied by fever, chills and aching muscles, severe blisters and bleeding in the lips, eyes, mouth, nose and genitals, worsening asthma and swelling of the face, legs, ankles and feet.
- Common adverse events include diarrhoea, nausea, dizziness and somnolence.

d) the dosage, formulation, labelling, packaging and presentation of a substance:

- Available in Australia as an oral dose form – Stromectol 3mg tablets.
- Also available as a topical formulation.

e) the potential for abuse of a substance:

- Nil

f) any other matters considered necessary to protect public health:

- Appendix D entry is consistent with current recommendations for clinical indications and COVID-19.
- If removed from Appendix D there is potential to lead to shortages.
- Patients not seeking (or delay in seeking) appropriate medical treatment if infected with COVID-19.
- Allowing appropriate supplies for approved conditions.

Reasons for the interim decision (including findings on material questions of fact)

I have made an interim decision to not amend the current Poisons Standard in relation to ivermectin. In consideration of the criteria under section 52E of the Act that I am required to consider, my decision turns principally on the risks and benefits to the public in accordance with paragraph 52E(1)(a) of the Act, as well as paragraph 52E(1)(c) regarding the toxicity of the substance. Specifically, there is a lack of safety and efficacy data to support both the long-term and frequent use of ivermectin for unapproved indications, including the prophylaxis and treatment of COVID-19. This leads to my view that the current scheduling of ivermectin and its inclusion in Appendix D is appropriate because there is insufficient evidence for benefit in relation to COVID-19 and significant risk. The detailed reasons for my decision follow.

I agree with the Committee's findings on the relevant provisions of section 52E of the Act.

I acknowledge the applicant's position that the current health climate in Australia has changed since the making of the decision in September 2021. The Appendix D entry was introduced due to the significant public health risks to an individual, and those around them, associated with taking ivermectin in an attempt to prevent COVID-19 infection rather than getting vaccinated, the unsafe dosages being promoted, and to ensure continued access for those who need the medicine for the treatment of scabies and parasitic infections.

In contrast to circumstances when I made my decision in September 2021, there are now high levels of vaccination within Australia and several approved treatments for COVID-19 available. The TGA has provisionally determined and registered 8 COVID-19 treatments,[29,30] including antivirals, immune modulators and monoclonal antibody treatments. Nevertheless, I continue to be concerned that the removal of the Appendix D entry may result in patients who are unwell with COVID-19 substituting ivermectin for approved therapies or, less so, vaccination. I remain of the opinion that there is a significant public health risk to an individual and those around them were ivermectin to be taken to prevent or treat COVID-19 infection, rather than using approved treatments.

In relation to paragraphs 52E(1)(a) and (f) of the Act, the Appendix D entry accords with the view of key national and international institutions about the use of ivermectin for the treatment and prophylaxis of COVID-19. The National Covid Evidence Taskforce (NCET) is an independent group of Australian clinical experts that undertakes continuous evidence surveillance to identify and rapidly synthesise emerging research to provide national, evidence-based guidelines for clinical care of people with COVID-19. The NCET advises against the use of ivermectin for

[29] https://www.tga.gov.au/products/covid-19/covid-19-treatments/covid-19-treatments-provisional-determinations

[30] https://www.tga.gov.au/products/covid-19/covid-19-treatments/covid-19-treatments-provisional-registrations

COVID-19 treatment outside of properly conducted clinical trials with appropriate ethical approval, and strongly discourages the use of ivermectin for the prevention or treatment of COVID-19.[31] Furthermore, the Cochrane Collaboration, the preeminent independent international body responsible for assessing clinical evidence for medical treatments and therapies, published a report stating that the available evidence for ivermectin is of low to very low quality and is insufficient to come to any clinically meaningful conclusions, and does not support the use of ivermectin for treating COVID-19 or preventing SARS-CoV-2 infection.[32] Several international regulators and COVID-19 taskforces do not support the use of ivermectin in patients for the prophylaxis and treatment of COVID-19 outside of clinical trials, including the World Health Organization, [33] the United States Food and Drug Administration, [34] the National Institute of Health (supported by the COVID-19 Treatment Guidelines Panel), [35] the Indian Council of Medical Research (ICMR) COVID-19 National Task Force Joint Monitoring Group, and the European Medicines Agency (endorsed by the COVID-19 EMA pandemic Task Force). [36]

I have taken into account all the public submissions received during the pre-meeting consultation period. I note the 17 written public submissions received during the pre-meeting consultation, including from the Australian Medical Network (AMN, formerly the COVID-19 Medical Network), the NSW Poisons Information Centre (NSW PIC), the Australian Society of Medical Practitioners (ASMP), the Society of Hospital Pharmacists of Australia (SHPA), Pharmaceutical Society of Australia (PSA), and the Pharmacy Guild of Australia (the Guild). In making this decision, I also note no submissions supporting the Proposal were submitted from key peak bodies, such as the Royal Australian College of General Practitioners, the Australian Medical Association, and the Australasian Society for Infectious Diseases.

Turning my mind to paragraph 52E(1)(b) of the Act, I have considered the purposes for which ivermectin is to be used. I note the many studies supplied by the applicant, the AMN, and the ASMP that suggest established efficacy of ivermectin against COVID-19, but agree with the Committee's view that the clinical data supporting use are small (some neither controlled, nor peer-reviewed, or published), and with various outcomes and endpoints. A large proportion of the studies provided are conducted in countries with dissimilar standards of medical care compared to Australia[37] and, contrary to what is stated, ivermectin is not, when considering the totality and quality of all available evidence, proven to be effective for preventing or treating COVID-19.

This is consistent with the consensus view of major regulators and in top-tier international medical journals that the evidence for the clinical efficacy and safety of ivermectin for the treatment or prevention of COVID-19 is not strong. There have been numerous trial-by-trial

[31] https://clinicalevidence.net.au/faqs/covid/

[32] Popp M, Stegemann M, Metzendorf M-I, et al. Ivermectin for preventing and treating COVID-19. Cochrane Database of Systematic Reviews 2021, Issue 7. Art. No.: CD015017. DOI: 10.1002/14651858.CD015017.pub2.

[33] https://www.who.int/news-room/feature-stories/detail/who-advises-that-ivermectin-only-be-used-to-treat-covid-19-within-clinical-trials

[34] https://www.fda.gov/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19

[35] https://www.covid19treatmentguidelines.nih.gov/therapies/miscellaneous-drugs/ivermectin/

[36] https://www.ema.europa.eu/en/news/ema-advises-against-use-ivermectin-prevention-treatment-covid-19-outside-randomised-clinical-trials

[37] Meyerowitz-Katz G, Wieten S, Medina Arellano M d J , et al. Unethical studies of ivermectin for covid-19 BMJ 2022; 377 :o917 doi:10.1136/bmj.o917

analyses of bias in clinical trials of ivermectin for COVID-19,[38,39,40,41,42] with one of the larger studies (cited by many subsequent studies) being withdrawn from preprint.[43,44] Concurrently, the results of large clinical studies investigating ivermectin use against COVID-19 that do not support use in patients with COVID-19 have been published.[45,46,47] I also refer to the media statement from Merck,[48] one of the major manufacturing companies of ivermectin, publicly confirming that their analyses have identified no scientific basis for a potential therapeutic effect against COVID-19 from pre-clinical studies, nor meaningful evidence for clinical activity or clinical efficacy in patients with COVID-19 disease. As there is still no established therapeutic benefit of ivermectin the prophylaxis and treatment of COVID-19, I consider that the Appendix D entry should remain.

In line with the above, the current Appendix D entry does not preclude use of ivermectin as part of a clinical trial approved by, or notified to, the Secretary of the Australian Government Department of Health and Aged Care under the Act. The TGA is regularly meeting with researchers and industry regarding potential treatments for the prevention and treatment of COVID-19 in a variety of clinical settings. As such, the entry does not act as a barrier for further research on the use of ivermectin for COVID-19 prevention and treatment. I am in agreement with the Guild that it is appropriate to retain the current Appendix D entry until there is sufficient and definitive evidence that ivermectin is effective for the prevention or treatment of COVID-19.

In addition, whilst there is still limited-conflicting evidence that ivermectin is efficacious against COVID-19, it is important to ensure continued access of ivermectin for those who need the medicine for treatment of scabies and parasite infections. It is essential that the treatment of parasitic infections must not be impeded by any restriction placed on ivermectin access and thus, retaining the entry will allow appropriate supplies for approved conditions. This position is supported by the SHPA.

In relation to paragraphs 52E(1)(c) and (d) of the Act, the ivermectin dosing schedules promoted for use in COVID-19 are almost always higher in total dose administered than for TGA approved indications, for which there has been evaluated safety and efficacy. I have reflected on the statements from the applicant, AMN, and ASMP that the safety of ivermectin is well

[38] Garegnani LI, Madrid E, Meza N. Misleading clinical evidence and systematic reviews on ivermectin for COVID-19. BMJ Evidence-Based Medicine 2022;27:156-158.

[39] Popp M, Kranke P, Meybohm P, et al. Evidence on the efficacy of ivermectin for COVID-19: another story of apples and oranges. BMJ Evidence-Based Medicine 2022;27:187-188.

[40] Levin AT, Owusu-Boaitey N, Pugh S, et al. Assessing the burden of COVID-19 in developing countries: systematic review, meta-analysis and public policy implications. BMJ Global Health 2022;7:e008477.

[41] Bartoszko J J, Siemieniuk R A C, Kum E, et al. Prophylaxis against covid-19: living systematic review and network meta-analysis BMJ 2021; 373 :n949 doi:10.1136/bmj.n949

[42] Izcovich A, Peiris S, Ragusa M, et al. Bias as a source of inconsistency in ivermectin trials for COVID-19: A systematic review. Ivermectin's suggested benefits are mainly based on potentially biased results. J Clin Epidemiol. 2022 Apr;144:43-55. doi: 10.1016/j.jclinepi.2021.12.018. Epub 2021 Dec 18. PMID: 34933115; PMCID: PMC8684188.

[43] www.researchsquare.com/article/rs-100956/v3

[44] www.nature.com/articles/d41586-021-02081-w

[45] Naggie S, Boulware DR, Lindsell CJ, et al. Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2022;328(16):1595–1603. doi:10.1001/jama.2022.18590

[46] Reis G, Silva EASM, Silva DCM, et al. TOGETHER Investigators. Effect of Early Treatment with Ivermectin among Patients with Covid-19. N Engl J Med. 2022 May 5;386(18):1721-1731. doi: 10.1056/NEJMoa2115869. Epub 2022 Mar 30. PMID: 35353979; PMCID: PMC9006771.

[47] https://www.medscape.com/viewarticle/971936

[48] www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic/

documented, expressly demonstrated in the 2013 AusPAR publication.[49] While the AusPAR mentions administering three doses 60, 90 and 120 mg on different days as part of clinical trials, the focus of safety studies in these dosing trials is intended to unveil potential nervous system side effects. Furthermore, these doses were given to healthy young adult males who are not reflective of the majority of people who may be ill with, or seeking prophylaxis for, COVID-19. The dose for the approved treatment of parasitic infections is 3–15 mg depending on the patient's body weight and the parasite, and only a single dose of ivermectin is usually required for parasites such as onchocerciasis or strongyloidiasis, while for scabies two doses are given one or two weeks apart. In contrast, the COVID-19 treatment protocols proposed doses of 12 mg (irrespective of body weight) on five consecutive days.

Higher doses of ivermectin carry significant risk of adverse effects. Documented adverse events include nausea, vomiting, diarrhea, hypotension (low blood pressure), allergic reactions (itching and hives accompanied by fever, chills and aching muscles), severe blisters and bleeding in the lips, eyes, mouth, nose and genitals, oedema of the face, legs, ankles and feet, dizziness, ataxia, seizures, coma and even death. Since implementation of the Appendix D entry, the NSW PIC has received 35 calls regarding exposures to ivermectin inappropriately used for COVID-19 treatment or prevention, of which 17 calls were relating to veterinary products. In my mind, these reports demonstrate the continued demand from consumers for the inappropriate use of ivermectin, and the risk to the public when used for unapproved indications.

In light of the above, I have turned my mind to the considerations for amending Appendix D in the SPF. It is my opinion that ivermectin continues to pose a specific health risk that may be mitigated by restricting availability through specialist medical practitioners.

Taking into account all the factors I am required to consider under section 52E of the Act, I consider that the current scheduling of ivermectin in the Poisons Standard is appropriate. Ivermectin use for unapproved indications will continue to be limited to use in clinical trials, or when prescribed by an appropriate specialist physician.

2.3 Interim decision in relation to brimonidine

Proposal

The applicant proposed the creation of a new Schedule 2 entry for ophthalmic preparations containing not more than 0.025 per cent of brimonidine for adult use (the **Proposal**). The new entry would provide pharmacy access to certain ophthalmic products for the treatment of eye redness and minor irritations in adults aged 18 years and over.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard substantially in line with the Proposal as follows:[50]

Schedule 4 – Amend entry

BRIMONIDINE **except** when included in Schedule 2.

[49] https://www.tga.gov.au/resources/auspar/auspar-ivermectin

[50] Proposed additions are shown in green underlined font, proposed deletions are shown in red strikethrough font, and text without this formatting represents the current text in the Poisons Standard.

Schedule 2 – New entry

BRIMONIDINE in ophthalmic preparations for adult use containing not more than 0.025% of brimonidine.

Index – Amend Entry

BRIMONIDINE

Schedule 4
Schedule 2

Materials considered

In making this interim decision, the Delegate considered the following material:

- The application to amend the current Poisons Standard with respect to brimonidine (the **Application**);
- The 3 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**);
- The advice received from the 40th meeting of the Advisory Committee on Medicines Scheduling (the **Committee**);
- Subsection 52E(1) of the Act, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health;
- The SPF; and
- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that the scheduling for brimonidine be amended in the Poisons Standard in the manner set out in my interim decision.

The Committee also recommended an implementation date of **1 June 2023**.

Members agreed that the relevant matters under Section 52E(1) of the Act included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health.

The reasons for the advice included:

a) the risks and benefits of the use of a substance

Risks

– Risks are very low overall, but there is a risk of allergic reaction and use for conditions that require attention by a medical professional (which can be mitigated through appropriate labelling)

- Pain at the site of administration, nasopharyngitis, headache.

Benefits

- Minimal, but includes reduced rebound congestion compared to other ocular decongestants and minimal loss of effectiveness over time.

b) the purposes for which a substance is to be used and the extent of use of a substance

- At a strength of 0.025% to relieve eye redness of the eye due to minor irritations such as environmental allergies, dryness and fatigue in adults. Incidence of these conditions is unclear.
- Higher concentrations used for treatment of elevated intraocular pressure associated with open angular glaucoma or ocular hypertension.

c) the toxicity of a substance

- Pregnancy Category B3 – brimonidine is listed under Category B3 of the Prescribing Medicines in Pregnancy database which outlines that studies in animals have shown evidence of an increased occurrence of fetal damage, however, the significance of this in humans is uncertain.
- At the proposed concentration there is low risk of toxicity. However, use of the preparation at this concentration should be restricted to adults 18 years and over as the highest risk for toxicity is in small children.

d) the dosage, formulation, labelling, packaging and presentation of a substance

- 1.9 mg in 7.5 mL bottle with child resistant cap – highest risk in small children but low concentration
- 1 drop, four times a day, effect lessening by 6-8 hours but no tachyphylaxis or rebound over 28 days
- Labelling will state “if symptoms persist for more than 3 days seek medical advice” however, the product labelling may need to be modified to reflect the risk of undiagnosed ophthalmological emergencies such as acute closed angle glaucoma or infectious keratitis more accurately.

e) the potential for abuse of a substance

- Nil.

f) any other matters that the Secretary considers necessary to protect public health

- Packaging should indicate that the product is not for use in a painful red eye, but this can be managed as part of the product registration.

Reasons for the interim decision (including findings on material questions of fact)

I have made an interim decision to amend the current Poisons Standard in relation to brimonidine and create a new Schedule 2 entry for ophthalmic preparations containing no more than 0.025 per cent. The detailed reasons for my decision follow.

I agree with the Committee’s findings on the relevant provisions of section 52E of the Act.

In reaching my interim decision, I have considered the Submissions and note that all were in support of the Proposal.

With respect to paragraph 52E(1)(b) of the Act, the proposed brimonidine ophthalmic preparation containing 0.025% of brimonidine will be used to relieve redness of the eye due to minor irritations such as environmental allergies, dryness and fatigue in adults. Currently there are several brimonidine products that reside in Schedule 4 of the Poisons Standard at significantly higher strengths used for lowering elevated intraocular pressure and the treatment of glaucoma.

In relation to the Scheduling Factors for Schedule 2 in the SPF and paragraphs 52E(1)(a), (c) and (d) of the Act, I am in agreement with the Committee that brimonidine at a concentration of 0.025% has a limited risk of toxicity and provides a very low risk to patients when used for the relief of eye redness caused by environmental allergens. It is in my view that this condition is self-diagnosable and, as such, there is a limited risk of misdiagnosis of a condition that is more severe. As part of the Schedule 2 entry, I have included the specification for 'adult use'. The applicant has also outlined the intention for packaging to have child-resistant caps to mitigate potential accidental child exposure to the product.

In further consideration of paragraphs 52E(1)(d) and (f) of the Act, the applicant has also proposed labelling with "if symptoms persist for more than 3 days seek medical advice". I agree with the Committee's recommendation that the labelling should include "not for use in a painful eye", and information to reflect the risk of undiagnosed ophthalmological ailments such as acute closed angle glaucoma or infectious keratitis. Such labelling and packaging is required to ensure that timely medical advice is sought in the case of more severe indications. However, I am of the opinion that this is appropriately dealt with as part of the product registration process and therefore there is no requirement to amend the Poisons Standard in this regard.

In further consideration of paragraph 52E(1)(a) of the Act, I agree that the ophthalmic preparation of low concentration brimonidine will reduce rebound congestion compared to other ocular decongestants with minimal loss of efficacy over time, as is the issue with the current ophthalmic decongestants available in Australia (particularly alpha-1 adrenergic receptor agonists). In addition, as brimonidine is an alpha-2 adrenergic receptor agonist, the preparation may be better suited for ophthalmic decongestion over the current alternative preparations consisting of alpha-1 or mixed alpha-1/alpha-2 agonists. The benefits of increasing access to such preparations through a Schedule 2 entry outweigh the potential risks, all which I have considered when making my interim decision.

I note that all currently available products containing brimonidine for ophthalmic use are at a much higher concentration than the proposed 0.025% and currently fall into Schedule 4 of the Poisons Standard. The current products are approved to treat elevated intraocular pressure associated with open angular glaucoma or ocular hypertension. In contrast, I am satisfied that Schedule 2 is appropriate for preparations that would be marketed with the much lower concentration of brimonidine and for the treatment of minor conditions as reflected by the Proposal.

Brimonidine at the 0.025% concentration is available as an over-the-counter medicine in comparable overseas countries such as the USA and Canada. As such, supporting the proposed amendment will be in line with other international regulators.

Implementation date

1 June 2023

2.4 Interim decision in relation to fexofenadine

Proposal

The applicant has proposed an amendment to the Schedule 2 entry for fexofenadine to increase the pack size available for general sale from 5 dosage units to 10 dosage units, when labelled for the treatment of seasonal allergic rhinitis in adults and children aged 12 years and above (the **Proposal**).

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard substantially in line with the Proposal as follows:[51]

Schedule 4 – Amend entry

FEXOFENADINE **except**:

a) when included in Schedule 2;

b) in divided preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

   i) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and

   ii) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine;

c) for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

   i) in a primary pack containing 10~~5~~ dosage units or less and not more than 10~~5~~ days' supply; and

   ii) labelled with a recommended daily dose not exceeding 180 mg of fexofenadine; or

d) for the treatment of seasonal allergic rhinitis and children 6 years of age and over when:

   i) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and

   ii) labelled with a recommended daily dose not exceeding 60 mg of fexofenadine.

Schedule 2

FEXOFENADINE in preparations for oral use **except** in divided preparations:

[51] Proposed additions are shown in green underlined font, proposed deletions are shown in red strikethrough font, and text without this formatting represents the current text in the Poisons Standard.

a) for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

   i) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and

   ii) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine;

b) for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

   i) in a primary pack containing 10~~5~~ dosage units or less and not more than 10~~5~~ days' supply; and

   ii) labelled with a recommended daily dose not exceeding 180 mg of fexofenadine; or

c) for the treatment of seasonal allergic rhinitis and children 6 years of age and over when:

   i) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and

   ii) labelled with a recommended daily dose not exceeding 60 mg of fexofenadine.

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FEXOFENADINE

Schedule 4
Schedule 2

Materials considered

In making this interim decision, the Delegate considered the following material:

- The application to amend the current Poisons Standard with respect to fexofenadine (the **Application**);
- The 2 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**);
- The advice received from the 40th meeting of the Advisory Committee on Medicines Scheduling (the **Committee**);
- Subsection 52E(1) of the Act, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance;
- The SPF; and
- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that the scheduling for fexofenadine be amended in the Poisons Standard in the manner set out in my interim decision.

The Committee also recommended an implementation date of **1 June 2023**.

Members agreed that the relevant matters under Section 52E(1) of the Act included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance;

The reasons for the advice included:

a) the risks and benefits of the use of a substance

Risks

- There is no change to the safety, efficacy or quality of the product that impacts the overall risk profile as a consequence of the proposed change to the Poisons Standard.
- Comparative effects to sedating antihistamines with improved adverse effect profile.

Benefits

- Fexofenadine has a well-established and favourable safety profile for adults and children 12 years of age and over.

b) the purposes for which a substance is to be used and the extent of use of a substance

- Antihistamine for managing symptoms of hay-fever.
- Indicated for SAR with a daily dosing of 120 mg or 180 mg. Can also be used to manage a range of allergic conditions including urticaria and food allergies.

c) the toxicity of a substance

- Established lack of toxicity through numerous preclinical and clinical studies at and above the recommended 180mg daily dose. Toxicity is very low even with higher than recommended doses

d) the dosage, formulation, labelling, packaging and presentation of a substance

- Packaging will be consistent with other formulations in this schedule and include statements on the single approved indication (SAR) as well as advise against prolonged use.

e) the potential for abuse of a substance

- Nil.

f) any other matters that the Secretary considers necessary to protect public health

- Nil.

Reasons for the interim decision (including findings on material questions of fact)

I have made an interim decision to amend the current Poisons Standard in relation to fexofenadine. The detailed reasons for my decision follow.

I agree with the Committee's findings on the relevant provisions of section 52E of the Act.

In relation to paragraph 52E(1)(a) of the Act, I have concluded that there are meaningful benefits to the increased access provided by implementing the Proposal, namely greater convenience for consumers in treating SAR. I have considered the issues raised in the Submissions, with the Pharmacy Guild of Australia (the Guild) expressing opposition to the Proposal and the Pharmaceutical Society of Australia (PSA) expressing support.

Reflecting on paragraphs 52E(1)(a), (b) and (d) of the Act, I consider that preparations of fexofenadine can be supplied and made available for general retail sale as such preparations meet the requirements for 'reasonable safety' as outlined in the Handbook. I have taken into account the non-sedative effects of the medication and note that there are no significant health risks associated with long-term use of the medicine. As the symptoms of SAR are easily recognised, it is unlikely to be confused by the consumer with other more serious diseases or conditions. In most cases symptoms can be managed by the consumer without the need for medical intervention. I also note the concerns raised by the Guild relating to the risk of mismanagement or misdiagnosis if used to treat skin rashes and urticaria due to lack of health professional advice at the point of supply. However, I am of the view that consumers will seek medical advice if symptoms persist or when required. In addition, this risk can be further reduced by appropriate packaging and labelling including consultation with a health professional if directed by labelling.

In relation to paragraphs 52E(1)(c) and (d) of the Act, I note concerns raised by the Guild, regarding risks to pregnant consumers in the context of the current Category B2 rating, specifically that implementation of the Proposal will lead to reduced adherence to the Required Advisory Statements for Medicine Labels (RASML) for the substance. However, I agree with the Committee that fexofenadine has a well-established history of safe use and I note that comparable substances with Category B2 ratings are currently available for general sale. I am of the view that adequate labelling addressing safety and efficacy concerns can be applied as part of the product registration process to improve safety and quality use of the substance.

With regards to paragraph 52E(1)(d) of the Act, I agree with the Committee that the proposed pack size limit of 10 days' supply is appropriate for a medicine that falls within the other criteria of the existing Schedule 2 entry for fexofenadine. The proposed limit on supply is consistent with other medicines in the same class with fexofenadine.

I acknowledge concerns raised by the Guild relating to the associated risk of torsades de pointes for consumers with pre-existing heart conditions. However, there is insufficient evidence before me to adequately satisfy me that this potential risk to consumers is likely to materialise. I also consider that such patients will already be in consultation with their medical practitioner.

After careful consideration of the SPF and relevant paragraphs of subsection 52E(1) of the Act, I have made my interim decision and proposed an implementation date of 1 June 2023.

Implementation date

1 June 2023

2.5 Interim decision in relation to ibuprofen

Proposal

The applicant proposed the rescheduling from Schedule 3 to Schedule 2 of modified release ibuprofen in divided preparations containing 400 mg or less of ibuprofen, in a primary pack containing not more than 12 dosage units, when labelled with a recommended daily dose of 1200 mg or less of ibuprofen (the **Proposal**). This would enable patients over 12 years of age to access some preparations of modified release ibuprofen without prior consultation with a pharmacist.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to not amend the current Poisons Standard in relation to ibuprofen.

Materials considered

In making this interim decision, the Delegate considered the following material:

- The application to amend the current Poisons Standard with respect to ibuprofen (the **Application**);
- The 5 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**);
- The advice received from the 40th meeting of the Advisory Committee on Medicines Scheduling (the **Committee**);
- Subsection 52E(1) of the Act, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health;
- The SPF; and
- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that the current Poisons Standard entry for ibuprofen remains appropriate.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health.

The reasons for the advice included:

a) the risks and benefits of the use of a substance

Risks

- Increased risk to the elderly, those with cardiovascular disease, renal disease and asthma and a rare incidence of hypersensitivity reactions and liver damage.
- Increased risk of gastrointestinal bleeding in persons who have a past history of gastric bleeding, stomach ulcers or prolonged use of ibuprofen.

Benefits

- Use for relief of pain and fever is well established. Ibuprofen is well tolerated with an excellent safety profile at the current 1200 mg/day therapeutic dose and the 2400 mg/day prescription dose for immediate release preparations.
- A modified release tablet formulation may enable reduced dosage frequency.

b) the purposes for which a substance is to be used and the extent of use of a substance

- Short term treatment for the relief of mild to moderate pain and fever associated with colds and flu, headaches, back pain, muscular aches and pain, dental related pain, arthritis, primary dysmenorrhoea, and other inflammatory conditions.
- Widely used, already available as a Schedule 2 medicine for immediate release preparations.

c) the toxicity of a substance

- Risks with long term use and use in renal impairment. Toxicity expected to be equivalent to IR preparations (safe AUC and lower peak concentration).
- Minimal toxicity at recommended dosages for the short-term treatment of approved indications.

d) the dosage, formulation, labelling, packaging and presentation of a substance

- Currently there are several marketed products between the 200 mg and 400 mg doses that are potentially affected by the proposed amendment.
- The applicant is expecting to market a 300 mg MR preparation with a recommended daily dose of 600 mg/day in packs of 12.
- The proposed labelling of the new 300 mg MR preparation is clearly labelled as modified release and emphasises the longer duration of action. Additionally, the labelling includes information regarding the different dosing requirements for the MR preparation compared to the IR preparations.

e) the potential for abuse of a substance

- Nil.

f) any other matters that the Secretary considers necessary to protect public health

- Increasing ibuprofen toxicity in general and potential for patient confusion in a complex product landscape comprised of multiple products, with differing instructions with regards to number of tablets to be taken and frequency of administration.
- In addition to concerns about accidental overuse, introducing MR preparations to Schedule 2 may lead to increased exposure to MR ibuprofen when IR dose may have been sufficient.

Reasons for the interim decision (including findings on material questions of fact)

I have made an interim decision to not amend the current Poisons Standard in relation to modified release (MR) preparations containing 400 mg or less of ibuprofen of no more than 12 dosage units for children and adults aged 12 years and over. The detailed reasons for my decision follow.

I agree with the Committee's findings on the relevant provisions of section 52E of the Act.

In making my interim decision, I have considered the benefits and risks of the Proposal in conjunction with the toxicity of MR ibuprofen, for the purposes of paragraphs of 52E(1)(a) and (c) of the Act. I note that the Proposal would increase convenience for consumers, allowing them to take—without the supervision of a pharmacist at the point of purchase—ibuprofen (MR) twice daily as opposed to three times daily (for immediate release (IR) ibuprofen). However, I have a particular concern regarding the increased potential for dosing and administration errors were there to be an expanded variety of MR and IR preparations supplied as Schedule 2 medicines. This concern is shared by several peak bodies including the Pharmacy Guild of Australia and Pharmaceutical Society of Australia.

The potential for administration or dosing errors poses a significant risk to the elderly, and those with cardiovascular disease, renal disease and asthma. Additionally, there have been rare incidences of hypersensitivity reactions and liver damage associated with the substance. While I note that ibuprofen has a well-established safety profile, there is not currently sufficient data to support that the toxicity risks associated with prolonged use of MR ibuprofen are equivalent to IR preparations, nor that there is minimal toxicity for short-term treatment of approved indications at the current recommended dosages. The current available safety data, including that provided by the applicant, only address the suitability for down-scheduling of preparations of ibuprofen up to 300 mg, whereas the Proposal includes preparations containing up to 400 mg ibuprofen, without providing any corresponding supportive evidence. I am therefore not satisfied that the benefits of having increased access to MR ibuprofen outweighs the potential risks.

Highlighting my concerns regarding the potential increased risks of dosage and administration errors, data submitted by the NSW Poisons Information Centre (NSW PIC) showed that from January to August 2022, the centre received 2,741 calls regarding potential poison exposures with single agent ibuprofen products (excluding recalls). Of these calls, 1,142 (42%) were due to therapeutic dose and administration errors. I am of the view that incidences of these errors are likely to increase with an expanded Schedule 2 entry as proposed. Consequently, I consider that this potential for consumers to mistake MR preparations for IR preparations argues for continuing pharmacist intervention and consultation that is afforded by the current scheduling of ibuprofen.

Further to the safe use of the substance, I consider that oversight of a pharmacist is required to confirm that MR preparations captured by the Schedule 3 entry for ibuprofen are the appropriate treatment for the intended indication. At present, MR preparations registered on the Australian Register of Therapeutic Goods (ARTG) are indicated for the temporary relief of persistent pain and or/inflammation likely to last more than 6 hours, not for chronic pain. If the Proposal were to be implemented, consumers who only require a 200 mg preparation may, without pharmacist intervention, select a 300 mg or 400 mg MR preparation with the mistaken belief that a higher dose would be more effective. Thus, I consider that introducing MR preparations in Schedule 2 may increase exposure to MR ibuprofen when IR preparations may have been sufficient. Consequently, I do not believe that the Proposal meets the requirements for Schedule 2, as outlined in the SPF, due to the high potential for accidental misuse.

Further reflecting on the SPF factors for Schedule 2, I agree with the Committee that, in relation to the preparations that are proposed to be down-scheduled:

- Quality use of the medicine cannot be achieved by labelling and packaging alone and requires pharmacist intervention to mitigate any potential for harm resulting from inappropriate use; and

- The potential for harm from inappropriate use through unintentional use of MR instead of IR is high.

In relation to paragraphs 52E(1)(b) and 52E(2)(a) of the Act, I consider that the MR preparations align with the SPF factors for Schedule 3 as the 12-hourly dosing of the MR ibuprofen preparations are intended for the treatment of persistent pain. The potential confusion between 'persistent pain' and 'chronic pain' may result in the consumer taking the MR preparation for a longer period of time, increasing risks of the occurrence of adverse events due to prolonged use. As such, Schedule 3 is applied where pharmacist intervention is required as the medicine is intended for recurrent or subsequent treatment of a chronic condition. I agree with the Committee's concerns regarding the increased risk of renal impairment or gastrointestinal bleeding due to prolonged use of ibuprofen.

I note that the applicant submitted a similar proposal in February 2021, which was discussed at the ACMS meeting in June 2021. The proposal sought to amend the Schedule 2 entry for ibuprofen to include 600 mg MR preparations in a primary pack containing not more than 16 dosage units, when labelled 'not for the treatment of children under 12 years of age'. Following the public consultations on that proposal, the Delegate decided that the then current scheduling remained appropriate, citing concerns of inappropriate use associated with the MR preparation that are appropriately mitigated by the intervention of a pharmacist. I find that the majority of the reasons for that decision are relevant for the present proposal.

As I can see no clear or compelling reason to amend the current scheduling in relation to MR ibuprofen, but identified several risks associated with the proposed change, I am satisfied that the current scheduling of ibuprofen remains appropriate, and it is my interim decision that no change be made to the scheduling of MR ibuprofen.

2.6 Interim decision in relation to melatonin

Proposal

The applicant proposed the rescheduling of immediate release melatonin from Schedule 4 to Schedule 3 for the treatment of jetlag. The rescheduling would apply to divided preparations containing 5 mg or less of melatonin, in packs of no more than 10 dosage units, for adults aged 18 and over (the **Proposal**). This would allow access to melatonin for this indication, without a prescription, after consulting with a pharmacist.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard substantially in line with the Proposal as follows:[52]

Schedule 4

MELATONIN for human use **except** when included in Schedule 3.

Schedule 3 – Amend Entry

MELATONIN in:

a) modified release tablets containing 2 mg or less of melatonin for monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep for adults aged 55 or over, in packs containing not more than 30 tablets; or

b) immediate release preparations containing 5 mg or less of melatonin for the treatment of jet lag in adults aged 18 or over, in a primary pack containing no more than 10 dosage units.

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MELATONIN

Schedule 4
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Appendix H

Materials considered

In making this interim decision, the Delegate considered the following material:

- The application to amend the current Poisons Standard with respect to melatonin (the **Application**);
- The 6 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**);
- The advice received from the 40th meeting of the Advisory Committee on Medicines Scheduling (the **Committee**);
- Subsection 52E(1) of the Act, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health;
- The SPF; and
- The Handbook.

[52] Proposed additions are shown in green underlined font, proposed deletions are shown in red strikethrough font, and text without this formatting represents the current text in the Poisons Standard.

Summary of Committee advice to the Delegate

The Committee recommended that the Schedule 3 entry for melatonin in the Poisons Standard be amended in the same manner as set out in my interim decision.

The Committee also recommended an implementation date of **1 June 2023**.

Members agreed that the relevant matters under Section 52E(1) of the Act included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health.

The reasons for the advice included:

a) the risks and benefits of the use of a substance:

Risks

- Interaction with warfarin and other medications (CYP 450 interactions).

Benefits

- Use of immediate release melatonin to prevent or reduce jet lag in adults is supported by the Australian Therapeutic Guidelines (TG):
  "melatonin immediate-release 0.5 to 5 mg orally, taken on the plane at the bedtime of the final destination; continue for up to 3 subsequent nights"
- Availability of Schedule 3 product under pharmacist oversight should reduce the use of unapproved products and use of benzodiazepines, thereby reducing the risk of harm.
- Risk profile is well defined.

b) the purposes for which a substance is to be used and the extent of use of a substance:

- For self-management of jet lag which is a self-limiting condition.
- As an approved alternative to the increasing/ongoing use of unapproved products for jet leg, with associated risks.

c) the toxicity of a substance:

- Generally low toxicity.
- Treatment regimen is a short course that is unlikely to result in any long-term adverse effects.

d) the dosage, formulation, labelling, packaging and presentation of a substance:

- Given the varying levels of accessibility to melatonin for jet lag across the world, a pack size that enables treatment for both outgoing and return flights is appropriate.
- The Therapeutic Guidelines explicitly highlights the suitability of an immediate release formulation of melatonin over a sustained release formulation for jet lag.

e) the potential for abuse of a substance:

- Nil.

f) any other matters considered necessary to protect public health:

- Potentially alters epilepsy (seizure) threshold.
- Provides an Australian sourced alternative product.

Reasons for the interim decision (including findings on material questions of fact)

I have made an interim decision to amend the Poisons Standard and create a new entry in Schedule 3 for melatonin in immediate release preparations for the treatment of jet lag in adults.

I agree with the Committee's findings on the relevant provisions of section 52E of the Act.

I have considered the 5 written public submissions received during the pre-meeting consultation period, with 4 written responses being fully supportive of the Proposal and one opposed. Interested parties were also given the choice to select from options to indicate their support or opposition to the proposed amendment without providing a written component. The results were also mostly supportive of the Proposal.

In relation to paragraph 52E(2)(a) of the Act, I am satisfied that immediate release preparations of melatonin, when supplied for the treatment of jet lag in adults, meet the scheduling factors for Schedule 3 that are stated in the SPF. Jet lag is a self-limiting condition which does not require medical diagnosis. The supply of melatonin for jet lag is substantially safe with pharmacist intervention to reinforce the appropriate duration and frequency of use. The risk profile of melatonin is well defined and the adverse effects, interactions and contraindications are known, identifiable and manageable by a pharmacist.

In considering paragraph 52E(1)(a) of the Act, I am of the view that increased access to the immediate release form of melatonin by way of the amendment to the Poisons Standard in my interim decision will provide alternative treatment options for jet lag that would be of significant benefit to consumers.

Addressing paragraphs 52E(1)(a) and (c) of the Act, I am satisfied that the risks identified and discussed by the Committee of drug interactions affecting Cytochrome P450 (CYP450) enzymes and the potential of altering seizure thresholds, can be minimised with the oversight of a pharmacist.

In turning my mind to paragraphs 52E(1)(b) and (c) of the Act, I acknowledge that although the efficacy of melatonin for sleep is generally low, there is sufficient evidence of its benefit in the treatment of jet lag in adults at the proposed dose of 5 mg.[53, 54] An umbrella review has shown that 9 out of 10 trials found melatonin to be effective at doses from 0.5 to 5 mg, and that doses exceeding 5 mg did not show any increase in effectiveness.[53] I have reflected on the single written submission opposing the Proposal, stating that the marginal benefits of increasing the dosage from 2 mg to 5 mg are significantly outweighed by the associated risks due to safety concerns. I was not able to identify any evidence that highlights safety issues with the use of melatonin 5 mg in the treatment of jet lag. Therefore, I am of the opinion that the proposed dose

[53] Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. Cochrane Database Syst Rev 2002(2):CD001520

[54] Suhner A, Schlagenhauf P, Johnson R, et al. Comparative study to determine the optimal melatonin dosage form for the alleviation of jet lag. *Chronobiol Int* 1998;15(6):655-66.

of melatonin 5 mg for the treatment of jetlag, is both safe and sufficiently effective, and also consistent with the Australian Therapeutic Guidelines.[55]

In turning my mind to paragraph 52E(1)(d) of the Act, I consider that a pack size of 10 dosage units is appropriate for the treatment of jet lag. The Therapeutic Guidelines recommends melatonin to be taken on the plane at the bedtime of the final destination and to continue for up to 3 subsequent nights.[55] The varying accessibility to melatonin across different countries was also taken into consideration when determining the pack size. A pack size of 10 will allow for 4 tablets to be taken on consecutive days on an outgoing and return trip, with 2 extra tablets to accommodate for potential layovers or stopovers.

In relation to paragraphs 52E(1)(a) and (f) of the Act, I am of the view that amendment of the Poisons Standard as set out in my interim decision will favour consumers accessing immediate release preparations of melatonin for jet lag that are regulated by the TGA rather than those sourced via the internet from abroad. Since the melatonin content in internet-sourced preparations is unreliable[55] and the inconsistency of its dosage strength will likely impact the potential effects of melatonin, a move to consumers accessing TGA-regulated products will minimise the risks to individuals and public health.

In summary, in consideration of subsection 52E(1) of the Act, I consider that the benefits associated with the proposed Schedule 3 entry for melatonin outweigh any potential risks of the increased access that such an entry would afford to users of the substance. I agree with the Committee that there is no reason to delay inclusion of the proposed entry for melatonin in the Poisons Standard and have therefore decided on an implementation date of 1 June 2023.

Implementation date

1 June 2023

3. Interim decisions on proposed amendments referred to the Advisory Committee on Medicines and Chemicals Scheduling in joint session (Joint ACMS-ACCS #32, November 2022)

3.1 Interim decision in relation to green tea extract

Proposal

The applicant proposed that a new Schedule 2 entry be included in the Poisons Standard for green tea extract in certain preparations for internal use, unless they are labelled with specified warning statements (the **Proposal**). Implementation of a Schedule 2 entry would remove relevant products not bearing the specified warning labels from general sale.

[55] Psychotropic Expert Group. Overview of jet lag. Therapeutic Guidelines Complete 2021

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to not amend the current Poisons Standard in relation to green tea extract.

Materials considered

In making this interim decision, the Delegate considered the following material:

- The application to amend the current Poisons Standard with respect to green tea extract (the **Application**);
- The 8 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**);
- The advice received from the 32nd meeting of the Advisory Committees on Medicines and Chemicals Scheduling in joint session (the **Committee**);
- Subsection 52E(1) of the Act, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health;
- The SPF; and
- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that the current scheduling for green tea extract remains appropriate, on the basis that scheduling is not an appropriate mechanism to address the concerns raised in the application.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health.

The reasons for the advice included:

a) the risks and benefits of the use of a substance:

Risks

- Evidence that high doses of green tea extract are associated with reversible elevation of markers of hepatotoxicity, leading to rare case reports of liver failure and death.

Benefits

- Limited evidence of benefit.
- Camellia sinensis is rich in polyphenolic catechins which have antioxidant and anti-inflammatory activities.

- Green tea, when consumed at 'reasonable' dietary intake levels, appears to be safe in humans.

b) the purposes for which a substance is to be used and the extent of use of a substance:

- Products containing green tea extract as an active ingredient are purported to provide a range of health benefits. They are generally labelled with low-level claims, such as weight loss, fitness, "detox", and other related claims.

c) the toxicity of a substance:

- Liver toxicity; clinical presentation of elevated ALT, AST and liver lesions. Observed in rats, mice and dog studies, both sub-chronic and chronic.
- EU recommends a warning for pregnant persons, however data in relation to reproduction & development was not available.
- Consideration should be given to the actual use patterns, i.e. short term vs long term. Uncertainty in the risk due to lack of data on chronic use and use by different demographics.

d) the dosage, formulation, labelling, packaging and presentation of a substance:

- The breadth of green tea extract and content of EGCG in the products.
- Various presentations including liquids, loose powder, capsules and tablets with differing extraction techniques and compositions.
- Consider the EU warning re use in pregnancy, noting the TGA pregnancy database does not include green tea; caffeine may be the limiting factor.

e) the potential for abuse of a substance:

- Nil.

f) any other matters considered necessary to protect public health:

- The drug-food interface – public comment from industry indicates some are worried about blurring this interface.
- Dosage aspects of green tea extract supplements (foods as medicines).
- Public health messaging.
- Prescriber messaging.

Reasons for the interim decision (including findings on material questions of fact)

I have made an interim decision to not amend the current Poisons Standard in relation to green tea extract. The detailed reasons for my decision follow.

I agree with the Committee's finding about the relevant provisions of section 52E of the Act.

At the forefront of the decision not to schedule green tea extract in the Poisons Standard I have turned by mind to paragraphs 52E(1)(a), (b) and (c) of the Act. Green tea extract exhibits a relatively low risk to the public and has widespread use. The risk profile of green tea extract and its component substances has not been well established or defined. I find that there is insufficient information available to determine a therapeutic dose for green tea extract, and

there is great uncertainty around the component substance responsible the observed therapeutic effects. It is also unclear if the same component(s) responsible for the therapeutic effects of green tea extract are also responsible for the reported cases of liver toxicity. I have considered the Proposal in light of the scheduling factors for Schedules 2 and 3 in the SPF in accordance with paragraph 52E(2)(a) of the Act. Turning my mind to these factors, for the reasons above, the substance does not meet the scheduling factors for Schedules 3 or 2.

Moreover, in considering the risks of green tea extract for the purposes of paragraph 52E(1)(a) of the Act, I am not persuaded that there is sufficient emerging evidence of an association between hepatotoxicity and green tea extract, nor what types and properties of green tea extract pose a risk that warrants scheduling. Furthermore, there is a lack of evidence for the concentration at which any constituent component is likely responsible for liver injury. In view of this uncertainty, I consider that any potential benefits of the Proposal are outweighed by undesirable limitations on access to the substance for legitimate and safe purposes.

Although there are reports of liver toxicity associated with its use,[56] there is no conclusive evidence that confirms the adverse events are directly caused by green tea extract. Moreover, most cases of elevated markers shown in liver function tests from the consumption of green tea extract were found to be reversible on cessation of use.[57] Health Canada reported on 19 published international case reports of liver injury requiring hospital treatment after the use of green tea extract from 2008-17. In the majority of these cases, stopping the use of the product was the first line of treatment and resolved the presenting signs and symptoms of liver injury. In reviewing these reports, I recognise that there are challenges in confirming the causes of liver toxicity from the consumption green tea extract and its corresponding concentrations that are deemed to be toxic. I also observe that in cases where there is a probable link between green tea extract and liver toxicity, the patient had a positive outcome.

As products are generally extracted from a cultivated herbal crop, it is also likely that the constituents of an extract of green tea will fluctuate from manufacturer to manufacturer and even from batch to batch. Taking into consideration the relatively low incidence of adverse events, I am not persuaded to implement the Proposal until more is known about the identity and dose of constituents responsible for hepatotoxicity that may warrant control through scheduling.

I note the Committee discussions on the possibility of creating a scheduling entry in relation to green tea extract's most abundant and biologically active antioxidant, epigallocatechin gallate (EGCG), as proposed by the applicant. I concur with the Committee that there is insufficient evidence confirming EGCG to be the key substance responsible for causing adverse liver events. As such, I do not consider that there is sufficient data for a safe dosage or scheduling of green tea extract, or EGCG, at this time.

In regard to paragraph 52E(1)(d) of the Act, there has not been an established therapeutic dose for green tea extract. This is complicated by the fact that green tea extract presents in many different compositions depending on the preparation and extraction methods used.[58] I share the view of the Committee that if scheduling of EGCG was considered, there is limited evidence to determine an appropriate therapeutic dose or unsafe dose.

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56 TGA, 'Green tea extract (Camellia sinensis) and hepatotoxicity: Pharmacovigilance and Special Access Branch safety review', 2018.

57 Health Canada. 'Signal Assessment: Green Tea Extract (GTE) (*Camellia sinensis* Leaf Extract) Risk of Hepatotoxicity (Liver Injury)', 2017.

58 Kim, Y-K., et al. 'Chemical Composition of Green Teas According to Processing Methods and Extraction Conditions'. Food Sci. Biotechnol. 2009; 18(5): 1212 -1217.

I am satisfied that until a time when there is more certainty on the identity and dose of constituent(s) within green tea extracts responsible for the reported adverse liver events, the potential risks raised from the consumption of green tea extract can be sufficiently mitigated by other mechanisms such as health practitioner messaging, public health messaging and requirements on product labelling imposed by the relevant regulators for foods and therapeutic goods.

4. Interim decisions on proposed amendments referred to the Advisory Committee on Chemicals Scheduling (ACCS #35, November 2022)

4.1 Interim decision in relation to ethalfluralin

Proposal

The applicant proposed new entries in Schedule 6 and Schedule 7 of the Poisons Standard for ethalfluralin (the **Proposal**). Specifically, the Proposal includes:

- A Schedule 6 entry for preparations containing ethalfluralin that are packed in bulk containers for specific use in closed mixing and loading agricultural equipment with a nominal capacity of 400 L or more; and
- A Schedule 7 entry for all other preparations.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in a manner that diverges from the Proposal, as follows:[59]

Schedule 7 – New entry

ETHALFLURALIN.

Index – New Entry

ETHALFLURALIN

Schedule 7

Materials considered

In making this interim decision, the Delegate considered the following material:

[59] Proposed additions are shown in green underlined font, proposed deletions are shown in red strikethrough font, and text without this formatting represents the current text in the Poisons Standard.

- The application to amend the current Poisons Standard with respect to ethalfluralin (the **Application**);
- The public submission received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations (the **Submissions**);
- The advice received from the 35th Meeting of the Advisory Committee on Chemicals Scheduling (the **Committee**);
- Subsection 52E(1) of the Act, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health;
- The SPF; and
- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that the Poisons Standard be amended in the same manner as my interim decision.

The Committee also recommended an implementation date of **1 June 2023**.

Members agreed that the relevant matters under Section 52E(1) of the Act included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health.

The reasons for the advice included:

a) the risks and benefits of the use of a substance:

Risks

- Toxicology profile that fits Schedule 7 in relation to genotoxicity, rather than acute toxicity.

Benefits

- Ethalfluralin is likely to play a role in resistance management and expected to offer an additional solution for controlling weeds in pulse crops.

b) the purposes for which a substance is to be used and the extent of use of a substance:

- The proposed use of ethalfluralin in Australia is for pre-plant weed control in pulse crops, mainly as an alternative to trifluralin.
- Ethalfluralin is proposed for use as an emulsifiable concentrate formulation containing 360 g/L ethalfluralin

c) the toxicity of a substance:

- Local irritant to eye, lung, skin.
- Genotoxic (in vitro), carcinogen (animal model)

d) the dosage, formulation, labelling, packaging and presentation of a substance:

- Large volume (1000 L) containers for industrial use with supply of smaller volumes (400 L) proposed for specific use in closed mixing / loading agriculture equipment systems.
- The APVMA has undertaken workplace health and safety (WHS) and public health risk assessments, culminating in recommendations for health-based guidance values. A signal header and appropriate first aid instructions and safety directions are recommended for the product label.
- A signal header for the product label will be recommended following the Scheduling of ethalfluralin.

e) the potential for abuse of a substance:

- Nil.

f) any other matters considered necessary to protect public health:

- Suitable WHS considerations for the operators need to be in place when using the chemical. Not for domestic use.
- The potential carcinogenicity of ethalfluralin has been assessed by the US EPA and Health Canada PMRA and similar to APVMA, consider that ethalfluralin products can be used safely in agricultural applications, by adherence to product label instructions.

Reasons for the interim decision (including findings on material questions of fact)

I have made an interim decision to amend the current Poisons Standard in relation to ethalfluralin. The detailed reasons for my decision follow.

I agree with the Committee's findings on the relevant provisions of Section 52E of the Act. In making my decision, I have considered paragraphs 52E(1)(a), (c) and (d) of the Act as the key matters on which to base this interim decision.

Ethalfluralin is a dinitroaniline herbicide intended to be used in pre-planting weed control, particularly for pulse crops. Currently, there are no other established uses for the substance.

The submitted acute toxicity data showed low to moderate levels of acute toxicity via the oral and inhalational routes. The main toxicity concerns associated with exposure to ethalfluralin are significant skin irritation presenting with erythema and oedema, eye irritation and skin sensitisation. I agree with the Committee that these factors are consistent with a Schedule 6 classification.

I also concur with the Committee's concerns regarding the carcinogenic and genotoxic potential of ethalfluralin, and the risks associated with repeat and unprotected use. Carcinogenicity studies with ethalfluralin have shown dose-related increases in rat mammary tumours, and mutagenicity in *in vitro* studies (Ames test and chromosomal aberrations in Chinese Hamster Ovary (CHO) cells). In addition, while ethalfluralin was not considered to be a reproductive toxicant based on a multigeneration study in rats, exposure at non-maternally toxic doses was associated with increased incidence of abortions, external abnormalities and skeletal abnormalities and variations during developmental studies in rabbits. In the absence of evidence to the contrary, it must be assumed that these effects in animals are also relevant to humans. I am therefore of the view that these results strongly suggest ethalfluralin should only be handled

by trained and approved personnel, using adequate measures to minimise exposure to the substance. This is consistent with the SPF factors 2 and 3 for Schedule 7 poisons:

> ***The substance has a high health hazard.*** *The substance presents a severe hazard from repeated and unprotected use or a significant risk of producing irreversible toxicity, which may involve serious, acute or chronic health risks or even death if it is inhaled, taken internally or penetrates the skin.*
>
> ***The dangers of handling the poison are such that special precautions are required in its manufacture, handling or use.*** *The dangers associated with handling the substance are too hazardous for domestic use or use by untrained persons and warrant restrictions on its availability, possession or use.*

Based on these factors, I agree with the applicant and the Committee that ethalfluralin warrants a parent entry in Schedule 7 of the Poisons Standard.

I have considered the Proposal to create an additional Schedule 6 entry for ethalfluralin when presented in large containers (>400 L) for use in closed mixing and loading systems for agricultural use. I note that there is no precedent in the Poisons Standard for down-scheduling or providing an exemption for a Schedule 7 herbicide or similar substance based on a combined minimum container size and specific method of dispersal/application. Despite this, I acknowledge the conditions for use stipulated under the proposed Schedule 6 entry in the Proposal, including the potential mitigation of the risks to public health associated with the closed nature of the system for use of these preparations. However, in consideration of paragraph 52E(1)(d) of the Act, I agree with the Committee that there is significant uncertainty regarding the potential for exposure to the substance in this presentation, and by extension an unacceptable risk to human health.

I note that as a dedicated herbicide with no other established use, users of ethalfluralin are likely to already possess the authority granted by their jurisdictional regulator to handle Schedule 7 poisons and have suitable training and experience to do so. Therefore, with reference to paragraph 52E(1)(a) of the Act, I consider that the risks associated with the proposed Schedule 6 entry for ethalfluralin outweigh any potential benefits of the reduced barriers to access that such an entry would afford to users of the substance. I find that it is appropriate for ethalfluralin to be included in Schedule 7 of the Poisons Standard as a stand-alone entry.

I have noted that the Application included limited data regarding the genotoxicity of ethalfluralin. A more expansive dataset detailing this aspect of the substance would be considered in light of any future applications to reschedule ethalfluralin.

I agree with the Committee that there is no reason to delay inclusion of ethalfluralin in the Poisons Standard and have therefore decided on an implementation date of **1 June 2023**.

Implementation date

1 June 2023

4.2 Interim decision in relation to tigolaner

Proposal

The applicant has proposed the creation of two new entries in the Poisons Standard for the new veterinary pest control agent tigolaner (the **Proposal**). The Proposal is specifically comprised of

a new Schedule 5 entry for preparations containing 10 per cent or less of tigolaner, and a Schedule 6 entry for all other preparations.

Interim decision

Pursuant to regulation 42ZCZN of the **Regulations**, the **Delegate** has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard as follows:[60]

Schedule 6 – New Entry

TIGOLANER **except** when in Schedule 5.

Schedule 5 – New Entry

TIGOLANER in preparations containing 10% or less of tigolaner.

Index – New Entry

TIGOLANER

Schedule 6
Schedule 5

Materials considered

In making this interim decision, the Delegate considered the following material:

- The application to amend the current Poisons Standard with respect to tigolaner (the **Application**);
- The advice received from the 35th Meeting of the Advisory Committee on Chemicals Scheduling (the **Committee**);
- Subsection 52E(1) of the **Act**, in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance;
- The SPF; and
- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that the Poisons Standard be amended in the same manner as my interim decision.

Members agreed that the relevant matters under subsection 52E(1) of the Act include: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

[60] Proposed additions are shown in green underlined font, proposed deletions are shown in red strikethrough font, and text without this formatting represents the current text in the Poisons Standard.

The reasons for the advice included:

a) the risks and benefits of the use of a substance

Risks:

- Significant and extensive toxic effects.
- High potential for bioaccumulation.

Benefits:

- Novel acaricide and insecticide for use on domestic cats, with a lower level of resistance than currently available products.
- Longest acting flea and tick treatment in cats with treatment interval of 13 weeks.

b) the purposes for which a substance is to be used and the extent of use of a substance

- Tigolaner will be used as one of the active substances (with emodepside and praziquantel) in a product intended for domestic cats.
- The product is expected to be applied as a one-off application, or once every three months for the treatment & prevention of flea, ticks and mites, and treatment and control of intestinal worms in cats and kittens.

c) the toxicity of a substance

- Toxic effects including effects on the endocrine system, panleukopenia, potential effects on the seizure threshold, developmental, reproductive and maternal toxicity and teratogenicity.

d) the dosage, formulation, labelling, packaging and presentation of a substance

- The intended product will be supplied in capped and sealed pipettes containing 0.37 mL of the spot-on solution. Individual pipettes are thermoformed foil sealed in blister trays. The concentration of tigolaner in the product is 97.90 mg/mL (i.e. each pipette contains 36.22 mg of tigolaner).
- Administered topically as a one-off dose or at 3 monthly intervals.

e) the potential for abuse of a substance

- Nil

f) any other matters that the Secretary considers necessary to protect public health

- Nil

Reasons for the interim decision (including findings on material questions of fact)

I have made an interim decision to amend the current Poisons Standard to include new entries for tigolaner in Schedules 5 and 6 of the Poisons Standard. The principal matters on which my decision turns relate to the risks and benefits to the public for the purposes of paragraph 52E(1)(a) of the Act, as well as paragraph 52E(1)(c) regarding the toxicity of the substance. The detailed reasons for my decision follow.

I agree with the Committee's finding that the relevant provisions of section 52E of the Act. I note that no public submissions were received in response to the pre-meeting consultation, published on 1 September 2022 under regulation 42ZCZK of the Regulations

Tigolaner belongs to the chemical class of bispyrazoles. It is an acaricide and insecticide that acts by blocking gamma-aminobutyric acid (GABA) gated chloride channels in the nervous system. In relation to paragraphs 52E(1)(b) and (d) of the Act, the applicant has proposed the scheduling of tigolaner, an active constituent of a combination product, for the treatment and prevention of flea infestations, control of ticks and mites, and treatment and control of intestinal worms in cats and kittens. The product, yet to be registered for use in Australia by the Australian Pesticides and Veterinary Medicines Authority (APVMA), is proposed to contain tigolaner at a concentration of 9.8% w/v, in combination with two other active constituents, praziquantel and emodepside. The proposed product will be supplied in pipettes containing different volumes for three different weight ranges in animals. The product will contain 97.90 mg/mL tigolaner and will be administered topically as a one-off dose, or at 3 monthly intervals.

I have considered the toxicity of tigolaner in relation to paragraph 52E(1)(c) of the Act. The submitted acute toxicity data showed very low levels of acute toxicity via the oral and dermal routes (>2000 mg/kg bodyweight, no deaths). No data were currently available for potential acute toxicity via the inhalational route, but, given the physicochemical properties of the substance and the intended use of tigolaner, it is likely that this route is toxicologically insignificant. Furthermore, tigolaner was not found to be a skin or eye irritant, or to be a potential skin sensitiser.

In a battery of secondary and safety pharmacology studies, tigolaner had no adverse effects on human cardiac ion channels, cardiovascular function in telemetered dogs or basic CNS function in rats at the doses/concentrations tested. Tigolaner is a $GABA_A$ receptor agonist and decreased the PTZ seizure threshold in rats at high doses (≥300 mg/kg bw, gavage). Tigolaner was not found to adversely affect T-cell mediated humoral immune response when tested in rats at doses up to 30 mg/kg bw (gavage).

In repeat dose, toxicity studies in rodents and dogs, exposure to tigolaner resulted in adverse changes in circulating leukon (panleukopenia), liver, adrenal cortex, ovarian interstitial cells, thyroid glands, pituitary glands, and the male reproductive system.

In multigenerational studies adverse reproductive effects included failure to litter, post-partum deaths, adverse effects on body weight delayed attainment of air-righting reflex, adrenotoxicity, toxicity to the epididymal epithelium and ovarian toxicity. The LOAEL for systemic toxicity (adrenotoxicity), and reproductive toxicity (increased incidence of failure to litter in the second (F2) generation) was 1.25 mg/kg bw/d. The NOAEL for developmental effects was 1.25 mg/kg bw/d due to reduced body weight gain (F1 generation) and delayed attainment of air-right reflexes (F2 generation). All doses were given by oral gavage.

In a rat prenatal toxicity study, tigolaner exposure during the period of organogenesis resulted while in the presence of maternotoxicity (manifesting as severe effects on body weight), in embryolethality, reduced live litter size, reduced total litter weight and an increased incidence of cleft palate (LOAEL 30 mg/kg bw/d, gavage). In a rabbit prenatal toxicity study tigolaner exposure during the period of organogenesis resulted in non-adverse skeletal variations due to precocious ossification and maternotoxicity manifesting adverse effects on maternal body weight. The developmental NOAEL was 300 mg/kg bw/d (highest dose tested, gavage), whereas the maternal NOAEL was 30 mg/kg bw/d (lowest dose tested, gavage).

Tigolaner was not genotoxic. No long-term exposure/carcinogenicity studies were conducted, given that tigolaner is not intended for use in food-producing species.

Tigolaner is very slowly and incompletely excreted and has a high potential for bioaccumulation. Importantly, human dermal absorption is very low (0.011%). Appropriate labelling will be required by the veterinary chemicals' regulator when assessing potential products to ensure no significant, inappropriate off-target exposure, e.g. children and pregnant women, will occur.

Considering this toxicity profile, I agree with the Committee's advice that the substance best resides in Schedule 6 of the Poisons Standard. It was noted that the APVMA has concluded that the human health risk to this substance was acceptable according to the criteria stipulated in Section 5A of the *Agricultural and Veterinary Chemicals Code Act 1994* (Cth).

In considering the applicability of the Schedule 5 proposal for preparations containing tigolaner at a concentration below 10%, the toxicity data provided by the applicant have shown low acute oral and dermal toxicity and that it is unlikely to be a skin or eye irritant and was not a potential skin sensitiser. Moreover, at this concentration, the substance's hazardous properties (as noted above) and the likelihood of injury during handling, storage and use of capped and sealed pipettes for spot-on application, can be mitigated by appropriate packaging and label warnings.

In relation to paragraph 52E(1)(d) of the Act, the applicant has demonstrated that appropriate risk mitigation measures will be put in place for use of the registered product in Australia, accounting for the dosage (application rate), formulation, labelling, packaging and presentation of the tigolaner-containing product(s). As such, I am satisfied that a concentration limit of up to 10% is adequate to be included in Schedule 5, consistent with the SPF factors for chemicals.

In consideration to paragraph 52E (1)(e), I note that there is no risk of dependency, abuse, misuse or diversion into illicit use.

Implementation date

1 October 2023

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Reference/Publication #