



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

6 February 2020

## Mometasone

An [interim decision](#) on mometasone was published on the TGA website 6 June 2019. In accordance with Regulation 42ZCZQ of the *Therapeutic Goods Regulations 1990*, the delegate of the Secretary has reconsidered the interim decision after seeking advice from the Advisory Committee on Medicines Scheduling in November 2019. This application will proceed to a final decision, which will be published on the [TGA website](#) on 23 April 2020.

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 under regulation 42ZCZN in relation to proposed amendments to the current Poisons Standard which were referred to an expert advisory committee under subdivision 3D.2 of the Regulations in November 2019;
- 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 **5 March 2020**.

Persons making submissions are strongly encouraged to lodge submissions in an electronic format (word or unsecured PDF preferred) using the [public submission coversheet](#) available on the TGA's website. Where possible, submissions should be sent to the email address provided below:

- [medicines.scheduling@health.gov.au](mailto:medicines.scheduling@health.gov.au) (for submissions relating to interim decisions made in relation to proposed amendments referred to the Advisory Committee on Medicines Scheduling or the Advisory Committee on Medicines and Chemicals Scheduling in joint session).

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

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# 1. Interim decisions on proposed amendments referred to the Advisory Committee on Medicines Scheduling (ACMS #28, November 2019)

## 1.1. Interim decision in relation to sumatriptan

### Interim decision

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

#### Schedule 4 – Amend Entry

SUMATRIPTAN **except** when included in Schedule 3.

#### Schedule 3 – New Entry

SUMATRIPTAN for oral use when in tablets containing 50 milligrams or less per tablet and when in a pack containing not more than 2 tablets.

#### Appendix H – New Entry

SUMATRIPTAN

#### Index – Amend Entry

SUMATRIPTAN

Schedule 4

Schedule 3

Appendix H

### *Proposed date of effect of the proposed amendment*

1 February 2021

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

#### *Applicant's scheduling proposal and reasons for the proposal*

An application to amend the current Schedule 4 entry for sumatriptan and to create new Schedule 3, Appendix H and Appendix M entries for sumatriptan was considered.

The Applicant's proposed amendments to the Poisons Standard were:

#### Schedule 4 – Amend Entry

SUMATRIPTAN **except** when included in Schedule 3.

#### Schedule 3 – New Entry

SUMATRIPTAN for oral use in medicines for the acute relief of migraine attacks with or without aura in patients who have a stable, well-established pattern of symptoms when in tablets containing 50 milligrams or less per tablet and when sold in a pack containing not more than 2 tablets.

#### Appendix H – New Entry

SUMATRIPTAN

#### Appendix M – New Entry

SUMATRIPTAN – to be dispensed by a registered pharmacist who has assessed a patient's symptoms to be consistent with an acute, episodic migraine attack; and that assessment and supply is consistent with expected professional standards of practice and specifically related clinical support tools and resources; and that a history of migraine or acute migraine treatment

has ideally been verified e.g. via the patient's My Health Record, or through previous prescribing/dispensing.

The pharmacist will record the supply of this medicine in their dispensary software, and include the patient's name, address, date of birth and gender. The pharmacist will label product with patient's name and directions for use and date of supply. The pharmacist will upload a record of supply to the patient's My Health Record.

## **Index – Amend Entry**

### **SUMATRIPTAN**

Schedule 4

Schedule 3

Appendix H

Appendix M

The Applicant's main points provided in support of the proposed amendments were as follows:

- A fundamental requirement for the efficacy of triptans (5HT-1 agonists) in the acute treatment of migraine is to administer within one hour of the onset of migraine headache.
- The current restrictions in accessing these medications via prescription only, and the time delay in seeking a GP appointment, attending and then obtaining the required prescription (in addition to economic and physical access barriers) prevents these patients from achieving proper therapeutic benefit.
- Delay in treatment increases the risk of more severe and prolonged headache pain, increases risk of inappropriate simple analgesic use and risk of medication overuse headache, increases risk of progression to chronic migraine, and increases the economic and productivity costs to Australia.
- Pharmacists have appropriate skill and knowledge to appropriately assess the migraine symptoms and history of patients/consumers. They already support people experiencing migraine with advice and the provision of simple analgesics, however also being able to provide sumatriptan to an appropriate selection of people would minimise delays in treatment and improve health outcomes.
- The assessment and management of migraine, including treatment with triptans, is within the professional scope of practice – as is recognised through undergraduate education, post-registration professional development and practice, and the medication scheduling of triptans in comparable countries such as New Zealand, the United Kingdom (2006),<sup>1</sup> Sweden (2008), and Germany (2006).<sup>2</sup>
- Increasing the access to sumatriptan for acute migraine through rescheduling to Schedule 3 does not eliminate the availability through prescription from a person's general practitioner. Nor will it lead to the frequently decried 'fragmentation of care', with the obligations described in the proposed Appendix M statement.
- Down-scheduling will provide safe and timely access to sumatriptan for people suffering acute, episodic migraine.

#### *Current scheduling status*

Sumatriptan is currently listed in Schedule 4 of the Poisons Standard as follows:

### **Schedule 4**

SUMATRIPTAN

### **Index**

**SUMATRIPTAN**

<sup>1</sup> <https://www.pharmaceutical-journal.com/learning/learning-article/practice-guidance-published-on-the-over-the-counter-supply-of-sumatriptan/10022365.article?firstPass=false>

<sup>2</sup> [http://www.pharmatimes.com/news/triptan\\_for\\_migraine\\_goes\\_otc\\_in\\_germany\\_995858](http://www.pharmatimes.com/news/triptan_for_migraine_goes_otc_in_germany_995858)

## Schedule 4

Other triptans are listed in Schedule 4 of the Poisons Standard as follows:

### Schedule 4

ELETRIPTAN.

NARATRIPTAN.

RIZATRIPTAN.

ZOLMITRIPTAN.

### *Scheduling history*

In August 1992, sumatriptan was first considered by the Drugs & Poisons Schedule Standing Committee (DPSSC) at the 66<sup>th</sup> meeting. The Committee noted that the 157<sup>th</sup> Australian Drug Evaluation Committee (ADEC) meeting recommended approval for the registration of sumatriptan for the acute relief of migraine. The Committee decided to include sumatriptan in Schedule 4 (Prescription Only). Sumatriptan tablets (XXXXXXX) were first marketed in Australia in 1992.

In June 2005, the NDPSC considered a proposal to include 2 tablets x 50 mg or less of sumatriptan from Schedule 4 (Prescription Only) to Schedule 3 (Pharmacist Only). The Committee decided that the scheduling of sumatriptan in Schedule 4 remained appropriate at that time. The Committee's action item was to refer sumatriptan to the following meeting if post-meeting comments were received.

In June 2006, the NDPSC considered a proposal to include oral preparations of 50 mg sumatriptan in packs of 2 tablets for the treatment of migraine attacks in Schedule 3 and Appendix H of the Poisons Standard. The Committee decided to defer a decision on the rescheduling of sumatriptan until advice had been sought from the XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX.

In October 2006, the NDPSC considered a proposal to include oral preparations containing 50 mg or less of sumatriptan in packs containing 2 dosage units or less for the treatment of migraine attacks in Schedule 3 and Appendix H of the Poisons Standard. The Committee decided to defer a decision on the rescheduling and Appendix H listing of sumatriptan pending review of emerging safety data from the Adverse Drug Reactions Advisory Committee (ADRAC) regarding serotonin syndrome.

In February 2007, the NDPSC considered a proposal to include oral preparations containing 50 mg or less of sumatriptan in packs containing 2 dosage units or less for the treatment of migraine attacks in Schedule 3 and Appendix H of the Poisons Standard. The Committee decided that Schedule 4 remained appropriate given concerns, at the time, for the lack of a real public health need for increased access through down-scheduling and given the 'emergency supply' provisions already in place. The Committee noted that the scheduling of sumatriptan was not harmonised with New Zealand and that this was appropriate at the time.

### *Australian regulations*

- According to the [TGA Ingredient Database](#),<sup>3</sup> sumatriptan is:
  - Available for use as an Active Ingredient in: Biologicals, Export Only, Prescription Medicines;
  - Available for use as an Excipient Ingredient in: Biologicals, Devices, Prescription Medicines; and
  - Available for use as an Equivalent Ingredient in: Export Only, Prescription Medicines.
- There are 45 medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#)<sup>4</sup> that contain sumatriptan as an active ingredient. These include 40 prescription medicines and 5 export only medicines.

<sup>3</sup> <https://www.ebs.tga.gov.au/>

<sup>4</sup> ARTG Search Sumatriptan [https://tga-search.clients.funnelback.com/s/search.html?query=Sumatriptan&collection=tga-artg&start\\_rank=1](https://tga-search.clients.funnelback.com/s/search.html?query=Sumatriptan&collection=tga-artg&start_rank=1)

- Sumatriptan is not permitted to be included in listed medicines as it is not included in the current [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2019](#).<sup>5</sup>
- The [Prescribing medicines in pregnancy database](#)<sup>6</sup> classifies sumatriptan as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Sumatriptan	B3	Cardiovascular System	Antimigraine preparations	-
<p><b>Category B3</b> – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.</p> <p>Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.</p>				

- The [Medicines Advisory Statement Specification 2019 \(RASML No. 5 – Schedule 1\)](#)<sup>7</sup> does not require warning statements pertaining to sumatriptan to be included on the labelling as sumatriptan is a Prescription Only Medicine and RAMSL is not applicable.
- The [Database of Adverse Event Notifications \(DAEN\)](#)<sup>8</sup> contains 682 reports of adverse events for products containing sumatriptan as an active ingredient, with 616 reports where sumatriptan was the single suspected medicine. There were four (4) reports of deaths associated with sumatriptan use.
- There are no products containing sumatriptan listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#).<sup>9</sup>

#### *International regulations*

- In the United States (U.S.) sumatriptan is approved by the Food and Drug Administration (FDA) as a human prescription drug. In the U.S., sumatriptan products are available in tablet, injection, subcutaneous injection and nasal spray/powder dosage forms.<sup>10</sup> Sumatriptan (as sumatriptan succinate) was the first triptan approved by the FDA in 1992.<sup>11</sup>
- In Canada, sumatriptan has been used in therapeutics since the 1990's. In the Index of Published Newsletters Government of Canada, [sumatriptan \(or its salts\) can be seen in January 1995; 5\(1\) and August 1993; 3\(1\) Canadian Adverse Reaction Newsletter](#).<sup>12</sup> Sumatriptan is currently scheduled as a prescription drug in Canada and can be seen on Canada's Prescription Drug List for human use and veterinary use, with the effective date of 19 December 2013.<sup>13</sup>
- In the United Kingdom (U.K.), certain sumatriptan products (50 mg tablets) are available without prescription, while other products in different dosage forms (e.g. nasal spray or injections) are available as prescription medicines.<sup>14</sup> In March 2005, sumatriptan was considered for reclassification to Pharmacy medicine by the Committee on Safety of Medicines (UK).<sup>15</sup>

<sup>5</sup> Therapeutic Goods (Permissible Ingredients) Determination (No. 4) 2019 <https://www.legislation.gov.au/Details/F2019L01597>

<sup>6</sup> <https://www.tga.gov.au/prescribing-medicines-pregnancy-database>

<sup>7</sup> Therapeutic Goods (Medicines Advisory Statements) Specification 2019 <https://www.legislation.gov.au/Series/F2019L00213>

<sup>8</sup> DAEN Report Sumatriptan Accessed 26 Jul. 19, <https://apps.tga.gov.au/Prod/daen/daen-report.aspx>

<sup>9</sup> PUBCRIS Sumatriptan Search <https://portal.apvma.gov.au/pubcris>

<sup>10</sup> U.S. FDA National Drug Code Directory [https://www.accessdata.fda.gov/scripts/cder/ndc/dsp\\_searchresult.cfm](https://www.accessdata.fda.gov/scripts/cder/ndc/dsp_searchresult.cfm)

<sup>11</sup> Drugs@FDA: FDA Approved Drug Products

<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020080>

<sup>12</sup> Index of Published Newsletters, Government of Canada <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/health-product-infowatch/published-newsletters.html#a2>

<sup>13</sup> Government of Canada, Prescription Drug List <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/list.html#a2>

<sup>14</sup> UK Government, UK Medicines and Healthcare products Regulatory Agency (MHRA), <http://www.mhra.gov.uk/spc-pil/index.htm?seclLevelIndexChar=Sq%20-%20Su#retainDisplay>

<sup>15</sup> Medicines and Healthcare products Regulatory Agency (MHRA), UKPAR XXXXXXXXXXXX. <http://www.mhra.gov.uk/home/groups/par/documents/websitesresources/con2024095.pdf>

Sumatriptan has been available without prescription in the United Kingdom since April 2006. Sumatriptan is an active ingredient in several nationally authorised products in Europe.<sup>16</sup>

- [The European Chemicals Agency \(ECHA\)](#)<sup>17</sup> hazard classification and labelling for sumatriptan is as follows: *'Danger! According to the classification provided by companies to ECHA in **CLP notifications** this substance causes serious eye damage, is suspected of damaging fertility or the unborn child and is harmful to aquatic life with long lasting effects.'*
- In New Zealand, sumatriptan in the [Medsafe Classification Database](#) is currently classified as a prescription medicine except when specified as a restricted medicine as follows:<sup>18</sup>
  - for oral use in medicines for the acute relief of migraine attacks with or without aura in patients who have a stable, well-established pattern of symptoms when in tablets containing 50 milligrams or less per tablet and when sold in a pack containing not more than 2 tablets that has received the consent of the Minister or the Director-General to its sale as a restricted medicine.
- In June 2005, the New Zealand Medicines Classification Committee (NZ MCC) *'felt that there was need for an alternative over-the-counter treatment for migraine. It was noted that sumatriptan was [at the time] under review in Australia for reclassification'*. In June 2006, the NZ MCC considered the safety profile of sumatriptan (50 mg tablets) as investigated by the UK Medicines and Healthcare Products Regulatory Agency (MHRA). The Committee recommended at their 35th Meeting, the reclassification of sumatriptan from a prescription medicine to a restricted medicine (OTC).

#### *Summary of pre-meeting public submissions*

In response to [the notice published under regulation 42ZCZK](#) advising of the proposed amendment, five (5) submissions were received. Four (4) submissions supported the amendment, two (2) of these with caveats. One (1) submission opposed the amendment.

#### **The main points provided in support of the proposed amendment were:**

- A Schedule 3 entry with inclusion in Appendix M to ensure that the patient has had a formal diagnosis by a medical practitioner would be an appropriate change to scheduling. This would bring Australia into harmonisation with New Zealand where this substance has been available without prescription for some time without adverse consequences.
- The maximum quantity to be available under Schedule 3 will be 2 tablets of 50 mg, which will be sufficient for one episode of a migraine. This is the same as the quantity and strength available in New Zealand which has been available since at least 2007.
- The proposed Appendix M in which the pharmacist will verify the diagnosis of migraine by checking the patient's My Health Record for the prescription and dispensing of sumatriptan will adequately address the issue of migraine diagnosis by a pharmacist. If the patient does not have a My Health Record or has no previous prescription and dispensing of sumatriptan, they can attend a general practitioner for further investigation of their condition.
- The possibility of sumatriptan and serotonergic antidepressants causing serotonin syndrome is low and this submission argues that it can be managed by the pharmacist by completing Migraine Questionnaire and verifying other medicines a patient is using by consulting the patient's My Health Record.
- The use of the My Health Record to verify previous diagnosis of migraine and dispensing of sumatriptan is analogous to the Continued Dispensing<sup>19</sup> option where a pharmacist can supply a PBS maximum quantity of a statin or oral contraceptive pill if the patient has previously been dispensed these medicines.

<sup>16</sup> EMA 2015 List of nationally authorised medicinal products, Active substance: Sumatriptan  
[https://www.ema.europa.eu/en/documents/psusa/sumatriptan-list-nationally-authorised-medicinal-products-psusa/00002832/201409\\_en.pdf](https://www.ema.europa.eu/en/documents/psusa/sumatriptan-list-nationally-authorised-medicinal-products-psusa/00002832/201409_en.pdf)

<sup>17</sup> <https://echa.europa.eu/substance-information/-/substanceinfo/100.130.760>

<sup>18</sup> Medsafe Classification Database(NZ) Database updated 16 July 2019, <https://medsafe.govt.nz/profs/class/classintro.asp>

<sup>19</sup> <https://www.humanservices.gov.au/organisations/health-professionals/services/medicare/pbs-pharmacists/initiatives/continued-dispensing>



- Community pharmacies quite regularly have migraineurs who find themselves without a supply of sumatriptan. Pharmacists can provide these patients with such Schedule 3 preparations as metoclopramide + paracetamol (XXXXXXX) or prochlorperazine (XXXXXX) but not sumatriptan. Further, the already available products under Schedule 3 for symptomatic treatment of migraine headaches largely aim to relieve nausea or vomiting associated with the headache, with paracetamol possibly only offering some relief against the headache itself. Having 50 mg x 2 tablets sumatriptan available as a Schedule 3 medicine would improve accessibility to this substance especially in after-hours situations or rural and remote areas where access to a GP is not possible.

**The main points provided in support of the proposed, with caveats amendment were:**

- XXXXX supports increased access to zolmitriptan and sumatriptan for patients experiencing migraines. However, there should be safeguards to ensure that access to this medication does not delay more urgent care. For example, symptoms similar to those of a migraine may actually be the result of a brain tumour. There needs to be increased pharmacist education around how to accurately and confidently diagnose a migraine. Further, the new Schedule entries should specify a certain number of times a patient can purchase this medication until it is recommended to consult a medical practitioner.
- Overall, XXX believe sumatriptan can be included in Schedule 3 with additional controls. The proposed Appendix M controls are appropriate in mitigating the risks associated with the provision of this triptan without a prescription. However, there is an apparent lack of preparatory work on an appropriate pharmacist training package. Without discussions with the Applicant, we are unable to comment on whether advertising of sumatriptan is appropriate.

**The main points provided in opposition to the proposed amendment were:**

- NSW PIC regularly receive calls regarding exposures to triptan medications, and although not large in numbers, these calls are very likely to be symptomatic and require medical treatment. Over 60% of exposures to sumatriptan were symptomatic and 62 of the 92 exposures (67%) required medical treatment:

Sumatriptan exposures 06.01.14 to 15.10.19						
Count of Exposure type and symptoms of those exposures						
	Accidental	Adverse reaction	Deliberate-self poisoning	Intentional: other	Therapeutic error	Grand total
Asymptomatic	10		6	2	10	28
Not know if related	1	7	1			9
Related symptomatic	5	13	21	1	8	48
Symptoms unknown			3		1	4
Unrelated symptomatic				1	2	3
Grand total	16	20	31	4	21	92

- The ability of triptans to interact with other medications and existing medical conditions is likely to contribute to this increased incidence of symptomatic adverse reactions and poisoning



exposures.

- Wider availability as a Schedule 3 product will see an increased use of triptans in the community and growth in these numbers of adverse reactions and poisoning exposures. The very real possibility exists that these exposures will increase disproportionately to usage as community awareness grows and patients begin self-prescribing.
- Current regulations which allow for emergency supply to patients who have a clear history of dispensing are sufficient to ensure those patients in need are able to safely access their regular medication in times of need without increasing risk to the community.

#### *Summary of ACMS advice/recommendations to the Delegate*

The Committee recommended that the current Schedule 4 entry for sumatriptan be amended and new Schedule 3 and Appendix H entries be created in the Poisons Standard as follows:

#### **Schedule 4 – Amend Entry**

SUMATRIPTAN **except when included in Schedule 3.**

#### **Schedule 3 – New Entry**

**SUMATRIPTAN for oral use when in tablets containing 50 milligrams or less per tablet and when in a pack containing not more than 2 tablets.**

#### **Appendix H – New Entry (Divided view)**

**SUMATRIPTAN**

#### **Index – Amend Entry**

**SUMATRIPTAN**

Schedule 4

**Schedule 3**

**Appendix H**

The Committee also recommended an implementation date of 1 February 2021.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) the risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and 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 that the Secretary considers necessary to protect public health.

The reasons for the advice included:

52E(1) Considerations	Reasons
a – the risks and benefits of the use of a substance	<p><i>Benefits</i></p> <ul style="list-style-type: none"><li>• Sumatriptan provides effective treatment for acute episodic migraine</li><li>• Safe when used as directed</li><li>• Down scheduling would improve patient access, reduce treatment delay and improve patient quality of life</li></ul> <p><i>Risks</i></p> <ul style="list-style-type: none"><li>• There are possible vascular side effects associated with sumatriptan, including rare cases of vasospasm related symptoms causing peripheral vascular ischemia,</li></ul>

	<p>colonic ischemia.</p> <ul style="list-style-type: none"> <li>• There is a risk of delayed diagnosis and treatment of depressive and anxiety disorders associated with migraine, contraindications, drug interactions, adverse effects such as dyspnoea, inaccurate/inappropriate assessment by pharmacist. Increased pharmacist knowledge and development of migraine questionnaire by pharmacist professional bodies will help to mitigate the above risks.</li> <li>• Misuse by adolescents as efficacy of oral triptans has not been established in people aged 12-17 years. However, this risk will remain the same as prescribed by a medical practitioner.</li> </ul>
b – the purposes for which a substance is to be used and the extent of use of a substance	<ul style="list-style-type: none"> <li>• Acute episodic migraine treatment</li> <li>• Cluster headache</li> </ul>
c – the toxicity of a substance	<p><i>Contraindications:</i></p> <ul style="list-style-type: none"> <li>• severe or uncontrolled hypertension</li> <li>• ischemic heart disease</li> <li>• coronary vasospasm</li> <li>• cerebrovascular disease</li> <li>• peripheral vascular disease</li> <li>• basilar or hemiplegic migraine</li> <li>• pregnant or at risk for pregnancy</li> <li>• MAOI use</li> <li>• used another triptan or ergotamine/dihydroergotamine in the previous 24hrs</li> <li>• Drug interaction between triptans and selective serotonin reuptake inhibitors (SSRI)/selective norepinephrine reuptake inhibitor (SNRI), which can lead to serotonin syndrome. However, risk is low and recommendation is to monitor. Viewing patient medication history via My Health Record and the use of a 'Migraine Questionnaire' will help to mitigate this.</li> </ul> <p><i>Adverse effects:</i></p> <ul style="list-style-type: none"> <li>• Cardiovascular effects mild and transient chest symptoms not associated with electrocardiogram (ECG) changes or enzymatic evidence of myocardial ischemia</li> </ul>
d – the dosage, formulation, labelling, packaging and presentation of a substance	<ul style="list-style-type: none"> <li>• 50-100 mg of sumatriptan tablets for acute attacks of migraine</li> <li>• May repeat dose if symptoms recur. Dose is not to be repeated if the first dose is ineffective</li> <li>• Maximum daily dose of 300 mg/24 hours</li> </ul>
e – the potential for abuse of a substance	<ul style="list-style-type: none"> <li>• Overuse of triptans may be associated with medication overuse headache.</li> </ul>
f – any other matters that the Secretary	<ul style="list-style-type: none"> <li>• Other Schedule 3 substances indicated for migraine are</li> </ul>

considers necessary to protect public health	not in Appendix H <ul style="list-style-type: none"> <li>Committee advised that Appendix M was not required as sumatriptan meets the scheduling factors for a Schedule 3 medicine.</li> </ul>
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### *Delegate's considerations*

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to sumatriptan;
- Advisory Committee on Medicines Scheduling's (ACMS# 28) advice;
- The public submission by the [first closing date](#);
- Section 52E of the *Therapeutic Goods Act 1989*, 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 that the Secretary considers necessary to protect public health;
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- [Scheduling Handbook](#) (V 1.1, July 2019).

### *Reasons for the interim decision*

I agree with the Committee's finding that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and 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 that the Secretary considers necessary to protect public health.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the Scheduling Factors for Schedule 3 and 4.

I have made an interim decision to amend the Poisons Standard by creating a new Schedule 3 entry for sumatriptan and I have set out my reasons below.

Sumatriptan is indicated for administration with migraine symptom onset and time critical access is crucial for management of the condition. I am of the view that the down-scheduling of sumatriptan to Schedule 3 would improve timely access for patients with a confirmed diagnosis of migraine, thereby improving patient outcomes.

I find that sumatriptan meets the Schedule 3 Scheduling Factors in that it 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. I consider that sumatriptan is substantially safe with pharmacist advice, to ensure quality use under a Schedule 3 classification.

I have considered that there is the potential for harm and adverse effects if sumatriptan is used inappropriately. The use of sumatriptan at established therapeutic dosage levels may mask the symptoms or delay diagnosis of more serious conditions. Further, there is the potential for drug interactions between sumatriptan and other drugs. However, on balance, I consider the risk profile of sumatriptan is well defined and the adverse effects, interactions and contraindications are known, identifiable and manageable by a pharmacist and by the pack size limitation. I am of the view that risk reduction can be further mitigated by pharmacist counselling and if necessary verification of diagnosis by a medical practitioner.

I acknowledge that emergency supply provisions could be an option for timely migraine management. However, I am of the opinion that these provisions are more commonly used for conditions where

other over the counter medications are not available. Whilst I find that a consumer is able to identify the ailments or symptoms of acute episodic migraine, I am of the view that the diagnosis, medical management or monitoring of this medical condition should be undertaken by a pharmacist before this substance is dispensed.

In making my decision, I have considered a recommendation that the pack size should be restricted, with the inclusion of appropriate warning and cautionary statements (such as possible contraindications and risk of serotonin toxicity with overuse) on product labelling. For this reason, I have made the decision that the Schedule 3 entry will be appropriate to mitigate the risk concerning overuse.

I have decided on an implementation date of 1 February 2021 to allow the opportunity for sponsors to adhere to regulatory change. In particular, this implementation date will provide sponsors the opportunity to align labelling requirements, Required Advisory Statements for Medicine Labels (RASML) statements to be developed and allow for the development of education and training material to be provided to pharmacists.

As part of the review of the [Scheduling Policy Framework](#) (SPF), it was agreed that advertising of medicines containing Schedule 3 substances should be permitted unless there was reason not to. In order for these medicines to be lawfully advertised, they need to be included in Appendix H of the Poisons Standard. Having considered the matters set out in the [Guidelines for advertisements for medicines containing Schedule 3 substances](#),<sup>20</sup> I am satisfied that there are no foreseeable potential impacts on public health that would preclude advertising sumatriptan directly to consumers and have decided that it should be included in Appendix H.

I have considered that additional controls over access and training to enable sumatriptan to be provided by a pharmacist through inclusion in Appendix M may be relevant. However, I find that on balance, sumatriptan meets the Scheduling Factors for a Schedule 3 medicine in the SPF and the access controls in place for a Schedule 3 medicine are appropriate and sufficient to mitigate the risk of misuse. Therefore, I have made the decision not to include sumatriptan in Appendix M.

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<sup>20</sup> <https://www.tga.gov.au/sites/default/files/guidelines-advertisements-medicines-containing-schedule-3-substances.pdf>

## 1.2. Interim decision in relation to zolmitriptan

### Interim decision

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

#### Schedule 4 – Amend Entry

ZOLMITRIPTAN **except** when included in Schedule 3.

#### Schedule 3 – New Entry

ZOLMITRIPTAN for oral use when in tablets containing 2.5 milligrams or less per tablet and when in a pack containing not more than 2 tablets.

#### Appendix H – New Entry

ZOLMITRIPTAN

#### Index – Amend Entry

ZOLMITRIPTAN

Schedule 4

Schedule 3

Appendix H

### *Proposed date of effect of the proposed amendment*

1 February 2021

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

#### *Applicant's scheduling proposal and reasons for the proposal*

An application to amend the current Poisons Standard with respect to zolmitriptan was considered. The application proposed to amend the current Schedule 4 entry and to create new Schedule 3, Appendix H and Appendix M entries for zolmitriptan.

The Applicant's proposed amendments to the Poisons Standard were:

#### Schedule 4 – Amend Entry

ZOLMITRIPTAN **except** when included in Schedule 3.

#### Schedule 3 – New Entry

ZOLMITRIPTAN for oral use in medicines for the acute relief of migraine attacks with or without aura in patients who have a stable, well-established pattern of symptoms when in tablets containing 2.5 milligrams or less per tablet and when sold in a pack containing not more than 2 tablets.

#### Appendix H – New Entry

ZOLMITRIPTAN

#### Appendix M – New Entry

ZOLMITRIPTAN – to be dispensed by a registered pharmacist who has assessed a patient's symptoms to be consistent with an acute, episodic migraine attack; and that assessment and supply is consistent with expected professional standards of practice and specifically related clinical support tools and resources; and that a history of migraine or acute migraine treatment has ideally been verified e.g. via the patient's My Health Record, or through previous prescribing/dispensing.

The pharmacist will record the supply of this medicine in their dispensary software, and include the patient's name, address, date of birth and gender. The pharmacist will label product with patient's name and directions for use and date of supply. The pharmacist will upload a record of supply to the patient's My Health Record.

## **Index – Amend Entry**

### **ZOLMITRIPTAN**

Schedule 4

Schedule 3

Appendix H

Appendix M

The Applicant's main points provided in support of the proposed amendments were as follows:

- A fundamental requirement for the efficacy of triptans (5HT<sub>1</sub> agonists) in the acute treatment of migraine, is to administer within one hour of the onset of migraine headache.
- The current restrictions in accessing these medications via prescription only, and the time delay in seeking a GP appointment, attending and then obtaining the required prescription (in addition to economic and physical access barriers) prevents these patients from achieving proper therapeutic benefit.
- Delay in treatment increases the risk of more severe and prolonged headache pain, increases risk of inappropriate simple analgesic use and risk of medication overuse headache, increases risk of progression to chronic migraine, and increases the economic and productivity costs to Australia.
- Pharmacists have appropriate skill and knowledge to appropriately assess the migraine symptoms and history of patients/consumers. They already support people experiencing migraine with advice and the provision of simple analgesics, however also being able to provide zolmitriptan to an appropriate selection of people would minimise delays in treatment and improve health outcomes.
- The assessment and management of migraine, including treatment with triptans, is within the professional scope of practice – as is recognised through undergraduate education, post-registration professional development and practice, and the medication scheduling of triptans in comparable countries such as New Zealand, the United Kingdom (2006),<sup>21</sup> Sweden (2008), and Germany (2006).<sup>22</sup>
- Increasing the access to zolmitriptan for acute migraine through rescheduling to Schedule 3 does not eliminate the availability through prescription from a person's general practitioner. Nor will it lead to the frequently decried "fragmentation of care", with the obligations described in the proposed Appendix M statement.
- Down-scheduling will provide safe and timely access to zolmitriptan for people suffering acute, episodic migraine.

#### *Current scheduling status*

Zolmitriptan is currently listed in Schedule 4 of the Poisons Standard as follows:

### **Schedule 4**

ZOLMITRIPTAN

### **Index**

**ZOLMITRIPTAN**

Schedule 4

<sup>21</sup> <https://www.pharmaceutical-journal.com/learning/learning-article/practice-guidance-published-on-the-over-the-counter-supply-of-sumatriptan/10022365.article?firstPass=false>

<sup>22</sup> [http://www.pharmatimes.com/news/triptan\\_for\\_migraine\\_goes\\_otc\\_in\\_germany\\_995858](http://www.pharmatimes.com/news/triptan_for_migraine_goes_otc_in_germany_995858)

Other triptans are listed in Schedule 4 of the Poisons Standard as follows:

#### **Schedule 4**

ELETRIPTAN.

NARATRIPTAN.

RIZATRIPTAN.

SUMATRIPTAN.

#### *Scheduling history*

In November 1997, the NDPSC #15 noted that the Australian Drug Evaluation Committee (ADEC) at its 193<sup>rd</sup> meeting, had recommended that zolmitriptan be approved for registration for the treatment of migraine, with or without aura. The NDPSC decided to include a new entry in the Poisons Standard for zolmitriptan in Schedule 4 (Prescription Only).

In June 2006, October 2006 and February 2007, the NDPSC considered proposals to reschedule sumatriptan (another triptan) 50 mg in packs of two from Schedule 4 to Schedule 3 for the treatment of migraine attacks. The Committee decided Schedule 4 remained appropriate for sumatriptan, noting this was not harmonised with New Zealand.

In October 2009, the NDPSC considered the scheduling of zolmitriptan following New Zealand's Medicines Classification Committee (MCC) reclassification of zolmitriptan 5 mg nasal spray to a restricted medicine in New Zealand (equivalent to Australia's Schedule 3 Pharmacist Only Medicine). The NDPSC decided the scheduling of zolmitriptan in Schedule 4 remained appropriate, noting this was not harmonised with New Zealand.

#### *Australian regulations*

- According to the [TGA Ingredient Database](#),<sup>23</sup> zolmitriptan is:
  - Available for use as an Active Ingredient in: Biologicals, Export Only, Prescription Medicines;
  - Available for use as an Excipient Ingredient in: Biologicals, Devices, Prescription Medicines; and
  - Not available as an Equivalent Ingredient in any application.
- There are nine (9) medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#)<sup>24</sup> that contain zolmitriptan as an active ingredient. These include nine (9) prescription medicines.
- Zolmitriptan is not permitted to be included in listed medicines as it is not included in the current [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2019](#).<sup>25</sup>
- The [Prescribing medicines in pregnancy database](#)<sup>26</sup> classifies zolmitriptan as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Zolmitriptan	B3	Cardiovascular System	Antimigraine preparations	-
<b>Category B3</b> – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.				

<sup>23</sup> <https://www.ebs.tga.gov.au/>

<sup>24</sup> ARTG Search Zolmitriptan <https://tga-search.clients.funnelback.com/s/search.html?query=Zolmitriptan+&collection=tga-artg>

<sup>25</sup> <https://www.legislation.gov.au/Details/F2019L01597>

<sup>26</sup> <https://www.tga.gov.au/prescribing-medicines-pregnancy-database>



Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

- The [Medicines Advisory Statement Specification 2019 \(RASML No. 5 – Schedule 1\)](#)<sup>27</sup> does not require warning statements pertaining to zolmitriptan to be included on the labelling as zolmitriptan is a Prescription Only Medicine and RAMSL is not applicable.
- The [Database of Adverse Event Notifications \(DAEN\)](#)<sup>28</sup> contains 20 reports of adverse events for products containing zolmitriptan as an active ingredient, with 13 reports where zolmitriptan was the single suspected medicine. There were no reports of deaths associated with zolmitriptan use.
- There are no products containing zolmitriptan listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#).<sup>29</sup>

#### International regulations

- In Canada, zolmitriptan (or its salts) is currently scheduled as a prescription drug and can be seen on [Canada's Prescription Drug List](#) for human use and veterinary use (with the effective date of 20 December 2013).<sup>30</sup>
- In the United States (U.S.) zolmitriptan is approved by the Food and Drug Administration (FDA) as a human prescription drug and are available in oral tablet dosage forms.<sup>31</sup> Zolmitriptan was first approved by the FDA in 1997.<sup>32</sup>
- In Europe, zolmitriptan is nationally authorised in several countries<sup>33</sup> as a migraine relief medication. In the United Kingdom (U.K), Zolmitriptan is available as a prescription medicine.<sup>34</sup>
- [The European Chemicals Agency \(ECHA\)](#)<sup>35</sup> hazard classification and labelling for zolmitriptan is as follows: *'Warning! According to the classification provided by companies to ECHA in CLP notifications this substance is harmful if swallowed, may cause damage to organs, causes serious eye irritation, causes skin irritation and may cause respiratory irritation.'*
- In May 2009, New Zealand's Medicines Classification Committee considered zolmitriptan nasal spray at the 41<sup>st</sup> Meeting. The Committee's recommendation was to reclassify 5 mg zolmitriptan (single prefilled nasal spray) from prescription medicine to restricted medicine when sold in packs approved by the Minister or the Director-General for distribution as a restricted medicine. This recommendation was also to align with the over the counter (OTC) classification of sumatriptan (another triptan).<sup>36</sup> Zolmitriptan as a nasal spray became pharmacist-only medicine in New Zealand in February 2010.<sup>37</sup>
- In New Zealand, zolmitriptan, in the [Medsafe Classification Database](#), is currently classified as a prescription medicine except when specified in as a restricted medicine (equivalent to Schedule 3) as follows:<sup>38</sup>
  - Zolmitriptan in a pre-filled nasal spray device containing not more than 5 milligrams of zolmitriptan, for the acute relief of migraine attacks with or without aura in patients who have

<sup>27</sup> Therapeutic Goods (Medicines Advisory Statements) Specification 2019 <https://www.legislation.gov.au/Series/F2019L00213>

<sup>28</sup> DAEN Report Zolmitriptan Accessed 26 Jul. 19 <https://apps.tga.gov.au/Prod/daen/daen-report.aspx>

<sup>29</sup> PUBCRIS Zolmitriptan Search <https://portal.apvma.gov.au/pubcris>

<sup>30</sup> Government of Canada, Prescription Drug List <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/list.html>

<sup>31</sup> U.S. FDA National Drug Code Directory [https://www.accessdata.fda.gov/scripts/cder/ndc/dsp\\_searchresult.cfm](https://www.accessdata.fda.gov/scripts/cder/ndc/dsp_searchresult.cfm)

<sup>32</sup> Drugs@FDA: FDA Approved Drug Products

<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020768>

<sup>33</sup> EMA, 2017. List of nationally authorised medicinal products, Active substance(s): zolmitriptan [https://www.ema.europa.eu/en/documents/psusa/zolmitriptan-list-nationally-authorised-medicinal-products-psusa/00003150/201703\\_en.pdf](https://www.ema.europa.eu/en/documents/psusa/zolmitriptan-list-nationally-authorised-medicinal-products-psusa/00003150/201703_en.pdf)

<sup>34</sup> UK Government, UK Medicines and Healthcare products Regulatory Agency (MHRA), <http://www.mhra.gov.uk/spc-pil/index.htm?subsName=ZOLMITRIPTAN&pageID=SecondLevel>

<sup>35</sup> <https://echa.europa.eu/substance-information/-/substanceinfo/100.158.186>

<sup>36</sup> Minutes of the 41<sup>st</sup> meeting of the Medicines Classification Committee (NZ)- <https://medsafe.govt.nz/profs/class/Minutes/2006-2010/mccMin14May09.htm>

<sup>37</sup> Medsafe (NZ) Medicines classification update February 2010

<https://medsafe.govt.nz/profs/puarticles/medicines%20classification%20update.htm>

<sup>38</sup> Medsafe Classification Database(NZ) Database updated 16 July 2019, <https://medsafe.govt.nz/profs/class/classintro.asp>

a stable, well-established pattern of symptoms and when sold in a pack of not more than 2 devices approved by the Minister or the Director-General for distribution as a restricted medicine.

#### *Summary of pre-meeting public submissions*

In response to [the notice published under regulation 42ZCZK](#) advising of the proposed amendment, four (4) submissions were received. Three (3) submissions supported the amendment, two (2) of these with caveats. One (1) submission opposed the amendment.

#### **The main points provided in support of the proposed amendment were:**

- Zolmitriptan has been on the Australian market for many years and is a safe and effective substance. The adverse effect profile of zolmitriptan is well described and the lack of overt risk of harm from zolmitriptan use is supported by toxicological information and guidance publicly available online through the US National Library of Medicine Toxnet database (on toxicological data for related sumatriptan)<sup>39</sup> and the New Zealand National Poisons Centre TOXINZ database<sup>40</sup>. TOXINZ notes that “No toxic dose for zolmitriptan has been established. The highest single dose used in clinical trials was 50 mg in healthy subjects producing sedation in some cases”.
- It would be appropriate for consumers to access zolmitriptan under the Schedule 3 Appendix M criteria. The Appendix M criteria will ensure that consumers who have previously been diagnosed and treated with a triptan will be able to purchase from a pharmacy without prescription if they have been previously been diagnosed by a medical practitioner and trialled the substance.
- Pharmacists have appropriate skill and knowledge to appropriately assess the migraine symptoms and history of patients/consumers. They already support people experiencing migraine with advice and the provision of simple analgesics, however also being able to provide sumatriptan or zolmitriptan to an appropriate selection of people would minimise delays in treatment and improve health outcomes.
- Down-scheduling will provide safe and timely access to zolmitriptan for people suffering acute, episodic migraine.

#### **The main points provided in support of the proposed amendment with caveats were:**

- The XXX supports increased access to zolmitriptan and sumatriptan for patients experiencing migraines. However, there should be safeguards to ensure that access to this medication does not delay more urgent care. For example, symptoms similar to those of a migraine may actually be the result of a brain tumour. There needs to be increased pharmacist education around how to accurately and confidently diagnose a migraine. Further, the new Schedule entries should specify a certain number of times a patient can purchase this medication until it is recommended to consult a medical practitioner.
- Overall, XXX believes that zolmitriptan can be included in Schedule 3 with additional controls. The proposed Appendix M controls are appropriate in mitigating the risks associated with the provision of this triptan without a prescription. In many overseas countries, triptans have been safely and effectively rescheduled to non-prescription status for use in patients who have well established and stable pattern of symptoms of migraine attacks. However, they have concerns over the apparent lack of preparatory work on an appropriate pharmacist training package and without discussions with the applicant are unable to comment on the suitability of an Appendix H entry for zolmitriptan.

#### **The main points provided in opposition to the proposed amendment were:**

- NSW PIC regularly receive calls regarding exposures to triptan medications, and although not large in numbers, these calls are very likely to be symptomatic and require medical treatment (see table below noting it is for sumatriptan exposures):

<sup>39</sup> Sumatriptan - National Library of Medicine HSDB Database'. Available via: <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+7742>

<sup>40</sup> 'Zolmitriptan TOXINZ - Poisons Information'. Available via: <https://www.toxinz.com/Spec/1918366>.

**Sumatriptan exposures 06.01.14 to 15.10.19**  
**Count of Exposure type and symptoms of those exposures**

	Accidental	Adverse reaction	Deliberate-self poisoning	Intentional: other	Therapeutic Error	Grand Total
Asymptomatic	10		6	2	10	28
Not Known if Related	1	7	1			9
Related Symptomatic	5	13	21	1	8	48
Symptoms Unknown			3		1	4
Unrelated Symptomatic				1	2	3
Grand Total	16	20	31	4	21	92

- The ability of triptans to interact with other medications and existing medical conditions is likely to contribute to this increased incidence of symptomatic adverse reactions and poisoning exposures.
- Wider availability as a Schedule 3 product will see an increased use of triptans in the community and growth in these numbers of adverse reactions and poisoning exposures. The very real possibility exists that these exposures will increase disproportionately to usage as community awareness grows and patients begin self-prescribing.
- Current regulations which allow for emergency supply to patients who have a clear history of dispensing are sufficient to ensure those patients in need are able to safely access their regular medication in times of need without increasing risk to the community.

*Summary of ACMS advice/recommendations to the Delegate*

The Committee recommended that the current Schedule 4 entry for zolmitriptan be amended and new Schedule 3 entry be created in the Poisons Standard. The Committee advised that the Delegate consider the appropriateness of Appendix H.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (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 that the Secretary considers necessary to protect public health.

The reasons for the advice included:

52E(1) Considerations	Reasons
a – the risks and benefits of the use of a substance	<p><i>Benefits</i></p> <ul style="list-style-type: none"> <li>• Zolmitriptan provides effective treatment for acute episodic migraine</li> <li>• Requires accurate diagnosis, exclusion of contraindications and interactions and proper follow up</li> </ul>

	<ul style="list-style-type: none"> <li>Safe when used as directed</li> <li>Down scheduling would improve patient access, reduce treatment delay and Improve patient quality of life</li> </ul> <p><i>Risks</i></p> <ul style="list-style-type: none"> <li>There are possible vascular side effects associated with zolmitriptan, including rare cases of vasospasm related symptoms causing peripheral vascular ischemia, colonic ischemia.</li> <li>There is a risk of delayed diagnosis and treatment of depressive and anxiety disorders associated with migraine, contraindications, drug interactions, adverse effects such as dyspnoea, inaccurate/inappropriate assessment by pharmacist. Increased pharmacist knowledge and development of migraine questionnaire by pharmacist professional bodies will help to mitigate the above risks.</li> <li>Misuse by adolescents as efficacy of oral triptans has not been established in people aged 12-17 years. However, this risk will remain the same as prescribed by a medical practitioner.</li> </ul>
b – the purposes for which a substance is to be used and the extent of use of a substance	<ul style="list-style-type: none"> <li>Acute episodic migraine treatment</li> <li>Cluster headaches</li> </ul>
c – the toxicity of a substance	<p><i>Contraindications</i></p> <ul style="list-style-type: none"> <li>severe or uncontrolled hypertension</li> <li>ischemic heart disease</li> <li>coronary vasospasm</li> <li>cerebrovascular disease</li> <li>peripheral vascular disease</li> <li>basilar or hemiplegic migraine</li> <li>pregnant or at risk for pregnancy</li> <li>MAOI use</li> <li>used another triptan or ergotamine/dihydroergotamine in the previous 24hrs</li> <li>Drug interaction between triptans and selective serotonin reuptake inhibitors (SSRI)/selective norepinephrine reuptake inhibitor (SNRI), which can lead to serotonin syndrome. However, risk is low and recommendation is to monitor. Viewing patient medication history via My Health Record and the use of a 'Migraine Questionnaire' will help to mitigate this.</li> </ul> <p><i>Adverse effects</i></p> <ul style="list-style-type: none"> <li>Cardiovascular effects mild and transient chest symptoms not associated with electrocardiogram (ECG) changes or enzymatic evidence of myocardial ischemia.</li> </ul>
d – the dosage, formulation, labelling, packaging and presentation of a substance	<ul style="list-style-type: none"> <li>2.5-5 mg of zolmitriptan tablets for acute attacks</li> <li>May repeat dose if symptoms recur. Dose is not to be repeated if the first dose is ineffective</li> <li>Maximum daily dose of 10 mg/24 hours</li> </ul>

e – the potential for abuse of a substance	<ul style="list-style-type: none"> <li>Overuse of triptans may be associated with medication overuse headache.</li> </ul>
f – any other matters that the Secretary considers necessary to protect public health	<ul style="list-style-type: none"> <li>Other Schedule 3 substances indicated for migraine are not in Appendix H</li> <li>Committee advised that Appendix M was not required as zolmitriptan meets the scheduling factors for a Schedule 3 medicine</li> </ul>

### *Delegate's considerations*

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to zolmitriptan;
- Advisory Committee on Medicines Scheduling's advice;
- The public submissions received by the [first closing date](#);
- Section 52E of the *Therapeutic Goods Act 1989*, 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 that the Secretary considers necessary to protect public health;
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- [Scheduling Handbook](#) (V 1.1, July 2019).

### *Reasons for the interim decision*

I agree with the Committee's finding that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are: (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 that the Secretary considers necessary to protect public health.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the Scheduling Factors for Schedule 3 and 4.

I have made an interim decision to amend the Poisons Standard by creating a new Schedule 3 entry for zolmitriptan and I have set out my reasons below.

Zolmitriptan is indicated for administration with migraine symptom onset and time critical access is crucial for management of the condition. I am of the view that the down-scheduling of zolmitriptan to Schedule 3 would improve timely access for patients with a confirmed diagnosis of migraine, thereby improving patient outcomes.

I find that zolmitriptan meets the Schedule 3 Scheduling Factors in that it is not expected to produce dependency at either the established therapeutic dose or at suprathreshold doses. Where risk of misuse, abuse or illicit use is identified, the risk can be minimised through pharmacist-consumer consultation. I consider that zolmitriptan is substantially safe with pharmacist advice, to ensure quality use under a Schedule 3 classification.

I have considered that there is the potential for harm and adverse effects if zolmitriptan is used inappropriately. The use of zolmitriptan at established therapeutic dosage levels may mask the symptoms or delay diagnosis of more serious conditions. Further, there is the potential for drug interactions between zolmitriptan and other drugs. However, on balance, I consider the risk profile of zolmitriptan is well defined and the adverse effects, interactions and contraindications are known, identifiable and manageable by a pharmacist and by the pack size limitation. I am of the view that risk reduction can be further mitigated by pharmacist counselling and if necessary verification of diagnosis by a medical practitioner.

I acknowledge that emergency supply provisions could be an option for timely migraine management. However, I am of the opinion that these provisions are more commonly used for conditions where other over the counter medications are not available. Whilst I find that a consumer is able to identify the ailments or symptoms of acute episodic migraine, I am of the view that the diagnosis, medical management or monitoring of this medical condition should be undertaken by a pharmacist before this substance is dispensed.

In making my decision, I have considered a recommendation that the pack size should be restricted, with the inclusion of appropriate warning and cautionary statements (such as possible contraindications and risk of serotonin toxicity with overuse) on product labelling. For this reason, I have made the decision that the Schedule 3 entry will be appropriate to mitigate the risk concerning overuse.

I have decided on an implementation date of 1 February 2021 to allow the opportunity for sponsors to adhere to regulatory change. In particular, this implementation date will provide sponsors the opportunity to align labelling requirements, Required Advisory Statements for Medicine Labels (RASML) statements to be developed and allow for the development of education and training material to be provided to pharmacists.

As part of the review of the [Scheduling Policy Framework](#) (SPF), it was agreed that advertising of medicines containing Schedule 3 substances should be permitted unless there was reason not to. In order for these medicines to be lawfully advertised, they need to be included in Appendix H of the Poisons Standard. Having considered the matters set out in the [Guidelines for advertisements for medicines containing Schedule 3 substances](#), I am satisfied that there are no foreseeable potential impacts on public health that would preclude advertising sumatriptan directly to consumers and have decided that it should be included in Appendix H.

I have considered that additional controls over access and training to enable zolmitriptan to be provided by a pharmacist through inclusion in Appendix M may be relevant. However, I find that on balance, zolmitriptan meets the Scheduling Factors for a Schedule 3 medicine in the SPF and the access controls in place for a Schedule 3 medicine are appropriate and sufficient to mitigate the risk of misuse. Therefore, I have made the decision not to include zolmitriptan in Appendix M.



### 1.3. Interim decision in relation to calcifediol

#### Interim decision

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

##### **Schedule 4 – New Entry**

**CALCIFEDIOL** for human internal therapeutic use **except** in preparations containing 10 micrograms or less of calcifediol per recommended daily dose.

##### **Index – New Entry**

**CALCIFEDIOL**

Schedule 4

#### ***Proposed date of effect of the proposed amendment***

1 June 2020

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

##### *Applicant's scheduling proposal and reasons for the proposal*

An application to create a new Schedule 4 entry for calcifediol was considered.

The Applicant's proposed amendments to the Poisons Standard were:

##### **Schedule 4 – New Entry**

**CALCIFEDIOL MONOHYDRATE** for human internal therapeutic use **except** in preparations containing 10 micrograms or less of calcifediol monohydrate per recommended daily dose.

##### **Index – New Entry**

**CALCIFEDIOL MONOHYDRATE**

Schedule 4

The Applicant's main points provided in support of the proposed amendment are as follows:

- Vitamin D (in both the colecalciferol and ergocalciferol forms) has a well-established profile and history of use. Calcifediol is the immediate metabolite of colecalciferol and is the circulating form of Vitamin D in the human body.
- The TGA has identified that calcifediol provides the same health benefits as colecalciferol, however the potency appears to be approximately three times greater. The safe daily dosage recommended by the TGA after evaluation is <10 micrograms/day in comparison to the Vitamin D scheduling limit of <25 micrograms/day.
- Calcifediol, as a direct metabolite of colecalciferol, would fall within the current scheduling entry for Vitamin D; i.e. it would be unscheduled at a daily dose of less than 25 micrograms per day. However, a safety evaluation performed by the TGA showed that the safe dosage for calcifediol is less than 10 micrograms per day. As such, it is proposed that a separate schedule entry be created for calcifediol to restrict the daily dosage to less than 10 micrograms per day unless medically prescribed.

#### ***Current scheduling status***

Calcifediol monohydrate is not specifically scheduled in the current Poisons Standard. However, it is considered a derivative of vitamin D and is therefore covered by the existing schedule entries for Vitamin D.



Vitamin D is currently listed in Schedules 3 and 4 and Appendix H of the Poisons Standard as follows:

#### **Schedule 4**

VITAMIN D for human internal therapeutic use **except**:

- a) in preparations containing 25 micrograms or less of vitamin D per recommended daily dose; or
- b) when included in Schedule 3.

#### **Schedule 3**

VITAMIN D for human internal therapeutic use in preparations containing 175 micrograms or less of vitamin D per recommended single weekly dose **except** in preparations containing 25 micrograms or less of vitamin D per recommended daily dose.

#### **Appendix H**

VITAMIN D

#### **Index**

#### **VITAMIN D**

cross reference: COLECALCIFEROL, ERGOCALCIFEROL

Schedule 4

Schedule 3

Appendix H

Calcifediol monohydrate is also a metabolite of the scheduled substance colecalciferol. Colecalciferol is currently listed in Schedule 7 and Appendix J of the Poisons Standard as follows:

#### **Schedule 7**

COLECALCIFEROL for use as a rodenticide.

#### **Appendix J, Part 2**

COLECALCIFEROL

#### **Index**

#### **COLECALCIFEROL**

cross reference: CHOLECALCIFEROL

Schedule 7

Appendix J, Part 2

#### *Scheduling history*

While calcifediol monohydrate is not specifically scheduled in the Poisons Standard, it is covered by the existing scheduled entry for vitamin D.

In March 1972, the National Drugs and Poisons Schedule Sub-committee (PSSC) first consider the scheduling of vitamin D. The PSSC considered a recommendation from the Nutrition Committee to set a concentration limit of vitamin A and D. A new Schedule 4 entry for vitamin D was created as follows: 'VITAMIN D when the recommended daily dosage on the label exceeds 10 micrograms'.

In July 1972, the PSSC gave consideration to Canadian restrictions (1972) on vitamin A and D products containing more than 1000 units (25 micrograms) of vitamin D in a recommended daily dose (RDD) being classified as prescription only medicines. The Sub-Committee agreed that high dosage requirements should be under medical supervision and a new Schedule 4 entry was recommended for vitamin D when the RDD exceeded 25 micrograms.

In November 1986, the Drugs and Poisons Schedule Committee (DPSC) revised the vitamin D Schedule 4 entry to clarify that the entry applied not just to preparations containing vitamin D, but also to the substance itself. The vitamin D Schedule 4 entry was amended to read, 'VITAMIN D for human therapeutic use except in preparations containing 25 micrograms or less of vitamin D per recommended daily dose'.

In November 1994, the National Drugs and Poisons Schedule Committee (NDPSC) noted that the vitamin D entry was originally intended to apply to preparations for internal use and that vitamin D was used in ointments and creams in the form of fish liver oils. Therefore, the Committee amended the Schedule 4 entry to 'VITAMIN D for human internal therapeutic use **except** in preparations containing 25 micrograms or less of vitamin D per recommended daily dose'.

In October 2009, the NDPSC considered an application from XXXXXXXXXXXX to:

- i) Implement a concentration cut-off from Schedule 4 to Schedule 3 for preparations within a RDD of 125 micrograms or less (retaining the current exemption for preparations with an RDD of 25 micrograms or less); and
- ii) Include vitamin D in Appendix H.

The NDPSC Evaluation report, while noting that the Applicant had presented a convincing case for both the prevalence of vitamin D deficiency and the need to treat such a deficiency, had not adequately justified why a high dose vitamin D should be listed as a Schedule 3 item rather than Schedule 4. The Committee generally agreed that while it was desirable to have a high potency vitamin D oral preparation available in Australia, professional medical diagnosis and management was required to treat moderate to severe vitamin D deficiency with such preparations. The Committee therefore decided that the scheduling of vitamin D remained appropriate.

#### *Australian regulations*

- According to the [TGA Ingredient Database](#), calcifediol monohydrate is:
  - Available for use as an active ingredient in: Export Only, Listed Medicines;
  - Not available as a Homoeopathic Ingredient in Listed Medicines;
  - Not available as an Excipient Ingredient in any application; and
  - Not available as an Equivalent Ingredient in any application.
- According to the [TGA Ingredient Database](#), calcifediol is:
  - Not available as an Active Ingredient in any application;
  - Not available as an Excipient Ingredient in any application; and
  - Available for use as an Equivalent Ingredient in: Export Only, Listed Medicines.
- According to the [TGA Ingredient Database](#), colecalciferol is:
  - Available for use as an Active Ingredient in: Biologicals, Export Only, Listed Medicines, Over the Counter, Prescription Medicines;
  - Not available as a Homoeopathic Ingredient in Listed Medicines;
  - Available for use as an Excipient Ingredient in: Biologicals, Devices, Export Only, Listed Medicines, Over the Counter, Prescription Medicines;
  - Available for use as an Equivalent Ingredient in: Listed Medicines, Prescription Medicines.
- According to the [TGA Ingredient Database](#), ergocalciferol is available:
  - Available for use as an Active Ingredient in: Biologicals, Export Only, Listed Medicines, Over the Counter, Prescription Medicines;

- [illegible]

- [The European Chemicals Agency \(ECHA\)](#) hazard classification and labelling for calcifediol monohydrate is '*Danger! According to the classification provided by companies to ECHA in CLP notifications this substance is fatal if swallowed, is fatal in contact with skin, is fatal if inhaled, causes damage to organs through prolonged or repeated exposure, is suspected of damaging fertility or the unborn child and may cause long lasting harmful effects to aquatic life*'.
- Calcifediol is not available for use in New Zealand. However, [The New Zealand Medicines and Medical Devices Safety Authority \(MEDSAFE\)](#)<sup>47</sup>: Vitamin D for internal use in medicines containing more than 25 micrograms per recommended daily dose except in parenteral nutrition replacement preparations is a prescription medicine. Vitamin D for external use or for internal use in medicines containing 25 micrograms or less per recommended daily dose; or in parenteral nutrition replacement preparations is available under general sale.
- Calcifediol is available as a prescription medicine in Canada as XXXXXXXXX (calcifediol modified-release capsules, 30 mcg). It is a vitamin D3 analogue indicated for the treatment of secondary hyperparathyroidism (SHPT) in adults with Stage 3 or 4 chronic kidney disease (CKD) and low

<sup>42</sup> <https://www.legislation.gov.au/Details/F2019L01597>

44 <https://www.legislation.gov.au/Details/F2019L00213>

46 <https://portal.apvma.gov.au/pubcris:jsessionid=tF-iBx+Fycw-C5UUqpsHfLR->

<sup>47</sup> <https://www.medsafe.govt.nz/profs/class/classintro.asp>

serum 25-hydroxyvitamin D levels (less than 75 nmol/L (30 ng/mL) at initiation). Calcifediol is also included in [Health Canada's Prescription Drug List \(PDL\)](#)<sup>48</sup> and is available for use in [human](#)<sup>49</sup> and [veterinary](#)<sup>50</sup> products. In May 2019, Health Canada published a [Notice of Consultation on the Prescription Drug List Vitamin D](#)<sup>51</sup>. Proposal is to allow non-prescription status to products containing up to 62.5 micrograms or 2500 international units (IU)/day for oral use:

Current Listing		Proposed Listing
Drugs containing any of the following	Vitamin D	Vitamin D
Qualifier	In oral dosage form containing more than 1,000 International Units of Vitamin D per dosage form or, where the largest recommended daily dosage shown on the label would, if consumed by a person, result in the daily intake by that person of more than 1,000 International Units of Vitamin D	In oral dosage form containing more than 62.5 µg or 2,500 International Units of Vitamin D per dosage form or, where the largest recommended daily dosage shown on the label would result in the daily intake by that person of more than 62.5 µg or 2,500 International Units of Vitamin D
Effective date	2013-12-19	To be determined

- XXXXXXXXX is also available as a prescription medicine in the United States of America.

#### *Summary of pre-meeting public submissions*

In response to [the notice published under regulation 42ZCZK](#) advising of the proposed amendment, two (2) submissions were received. One (1) submission supported the amendment and one (1) submission opposed the amendment.

#### **The main points in support of the proposed amendment were:**

- Given the potency of calcifediol monohydrate has been identified to be approximately three times greater than colecalciferol, a lower limit of 10 micrograms (compared to the 25 micrograms for colecalciferol) to be applied to the Schedule 4 entry seems appropriate.

#### **The main points in opposition of the proposed amendment were:**

- Access to calcifediol monohydrate should not require a prescription. If there is a concern about the potency of this particular version of vitamin D, then a Schedule 3 listing would address these concerns by ensuring that pharmacists are involved in the sale and could reinforce the difference between this substance and other vitamin D preparations available on the market.
- Calcifediol monohydrate meets the Scheduling Factors for inclusion in Schedule 3:
  - it is a vitamin and is substantially safe with pharmacist intervention and counselling to ensure consumers are aware of the difference in potency compared to other products on the market;
  - it is not a drug of dependence, and there is no risk of abuse or illicit use. Inadvertent overdose can be managed with pharmacist involvement in its supply; and
  - the risk profile of vitamin D is well defined and can be managed by a pharmacist.

<sup>48</sup> <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list.html>

<sup>49</sup> <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/list.html#a1>

<sup>50</sup> <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/list.html#a2>

<sup>51</sup> <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/notices-changes/vitamin-d-notice-consultation-prescription-drug-list.html>

### Summary of ACMS advice/recommendations to the Delegate

The Committee recommended that a new Schedule 4 entry for calcifediol be created in the Poisons Standard as follows:

#### Schedule 4 – New Entry

**CALCIFEDIOL** for human internal therapeutic use **except** in preparations containing 10 micrograms or less of calcifediol per recommended daily dose.

#### Index – New Entry

**CALCIFEDIOL**

Schedule 4

The Committee also recommended an implementation date of 1 June 2020.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) the risks and benefits of the use of a substance; (b) the purpose 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:

52E(1) Considerations	Reasons
a – the risks and benefits of the use of a substance	<ul style="list-style-type: none"><li>Calcifediol has been shown to adequately raise serum 25-hydroxyvitamin D levels and has better oral bioavailability than other Vitamin D substances in current use. It is more potent than other Vitamin D substances in current use and may be more useful in patients with malabsorption diseases.</li><li>Calcifediol is pharmacodynamically similar to other Vitamin D substances and therefore would be expected to have similar adverse effects and drug interactions, supporting scheduling consistent with other Vitamin D substances.</li></ul>
b – the purposes for which a substance is to be used and the extent of use of a substance	<ul style="list-style-type: none"><li>Current consensus recommendation that Vitamin D supplementation should only be used where Vitamin D deficiency is confirmed is consistent with the medical oversight required by Schedule 4.</li></ul>
c – the toxicity of a substance	<ul style="list-style-type: none"><li>The effectiveness and by extrapolation the toxicity of calcifediol is calculated to be approximately three times the same dose of other Vitamin D forms available (colecalciferol and ergocalciferol).</li><li>Well known dose related toxicity which means medical monitoring and oversight is necessary, consistent with a Schedule 4 classification.</li></ul>
d – the dosage, formulation, labelling, packaging and presentation of a substance	<ul style="list-style-type: none"><li>Human studies confirm the safety of low daily dosing and support exemption from scheduling at a daily dose of 10 micrograms for adults.</li></ul>
e – the potential for abuse of a substance	<ul style="list-style-type: none"><li>Nil</li></ul>
f – any other matters that the Secretary considers necessary to protect public health	<ul style="list-style-type: none"><li>Nil</li></ul>

### *Delegate's considerations*

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to calcifediol;
- Advisory Committee on Medicines Scheduling's advice;
- The public submissions received by the [first closing date](#);
- Section 52E of the *Therapeutic Goods Act 1989*, 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 Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- [Scheduling Handbook](#) (V 1.1, July 2019).

### *Reasons for the interim decision*

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (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.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the Scheduling Factors for Schedule 4.

I have made an interim decision to amend the Poisons Standard by creating a new Schedule 4 entry for calcifediol and I have set out my reasons below.

I have considered that as a direct metabolite of and the circulating form of colecalciferol in the body, calcifediol would fall within the current Schedule 4 entry for Vitamin D and would be unscheduled at a daily dose of 25 micrograms per day. However, I am of the view that while the toxicity and safety markers for calcifediol can be considered the same as for colecalciferol, a separate scheduling entry is warranted due to their differing potencies. I note that calcifediol has been assessed by the TGA as safe at a daily dose of 10 micrograms or less, and this is significantly lower than the 25 micrograms per day recommended for colecalciferol. On balance I find the proposed 10 microgram daily dose cut-off is consistent with combined consideration of the three-fold potency of calcifediol compared to colecalciferol.

I have considered that there is a potential for drug interactions between Vitamin D substances and other drugs. Cytochrome P450 inhibitors such as ketoconazole, clarithromycin and various antiretroviral drugs may inhibit enzymes involved in Vitamin D metabolism and hence alter serum levels of calcifediol. As Cytochrome P450 3A4 (CYP3A4) is involved in Vitamin D metabolism, other medicines metabolised by this enzyme, such as statin drugs, may compete for enzyme activity with Vitamin D substances. Due to these potential interactions and subsequent adverse effects (particularly dose dependent adverse effects) means there remains a need to have a primary entry for any Vitamin D substance in Schedule 4. In view of this, recommendation that supplementation only be undertaken where a person has confirmed Vitamin D deficiency also supports a primary Schedule 4 entry for all Vitamin D substances, including calcifediol.

I find that a Schedule 4 entry with a 10 microgram daily dose cut-off to exempt from scheduling for calcifediol would be consistent with the current Schedule 4 entry for Vitamin D. Further, I find that it is important to specify internal use in humans as no information was presented regarding topical use and there has been no consideration of animal use.



## 1.4. Interim decision in relation to paracetamol (liquid formulations)

### Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the paracetamol (liquid formulations) as follows:

#### Schedule 3 – Amend Entry\*

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; or
- c) in liquid preparations for oral use **except** when in Schedule 2.

\*The proposed amended Schedule 3 entry for paracetamol as written includes the [final decision](#)<sup>52</sup> for modified paracetamol that will be implemented 1 June 2020.

#### Schedule 2 – Amend Entry

PARACETAMOL for therapeutic use:

- a) in liquid preparations for oral use containing a maximum of 10 g of paracetamol per container;
- 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 enclosed in a primary pack containing not more than 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 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 10 such powders or sachets of granules,
    - (B) compliant with the requirements of the Required Advisory Statements for Medicine Labels,

<sup>52</sup> <https://www.tga.gov.au/book-page/14-final-decision-relation-paracetamol-modified-release>



- (C) not labelled for the treatment of children 6 years of 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 20 tablets or capsules,
  - (C) compliant 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.

***Proposed date of effect of the proposed amendment***

1 June 2020

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

***Applicant's scheduling proposal and reasons for the proposal***

An application to amend the Schedule 2 and Schedule 4 entries for paracetamol was considered. The proposal sought to set limits on the volume of liquid paracetamol available for oral use.

The Applicant's proposed amendments to the Poisons Standard were:

**Schedule 4 – Amend Entry**

**PARACETAMOL:**

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

## Schedule 2 – Amend Entry

PARACETAMOL for therapeutic use:

- a) in liquid preparations for oral use containing no greater than 50 mg per mL of paracetamol in 100 mL with a maximum of 50 g paracetamol per container;
- 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 enclosed in a primary pack containing not more than 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 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 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 of 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 20 tablets or capsules,
    - (C) compliant 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.

The main points provided in support of the proposed amendments were as follows:

- The paracetamol entries in Schedules 2, 3 and 4 of the Poisons Standard aim to minimise the risk of accidental poisoning by limiting the total dose in a pack. However, there is no limit on the amount of paracetamol that can be supplied in the liquid form in Schedule 2.
- A product containing large quantities of paracetamol, particularly in liquid form, carries a potential for significant human toxicity (including delayed irreversible hepatotoxicity) if the product is accidentally ingested or deliberately misused.
- In view of the known risks of paracetamol toxicity to humans (the acute toxic effects include hepatic and renal tubular necrosis) and in the interests of public health, it is appropriate to limit the volume or maximum paracetamol mass in Schedule 2 paracetamol liquid preparations.
- Liquid paracetamol products are marketed in formulations containing:
  - 24 mg/mL paracetamol in 50, 100, 200 and 500 mL pack sizes;
  - 48 mg/mL paracetamol in 50, 100, 200 and 500 mL pack sizes;
  - 50 mg/mL paracetamol in 60, 100, 200 and 1000 mL pack sizes;
  - 100 mg/mL paracetamol in 5 and 20 mL pack sizes; and
  - 32.5 mg/mL paracetamol + 1 mg/mL dextromethorphan in 120, 240 and 360 mL pack sizes (intended primarily for use in children, are currently available as a Pharmacy Medicine (Schedule 2)).

#### *Current scheduling status*

Paracetamol is listed in Schedules 2, 3 and 4 and Appendix F and H of the current Poisons Standard 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;
- b) when combined with ibuprofen in a primary pack containing more than 30 dosage units;
- c) in slow release tablets or capsules containing more than 665 mg paracetamol;
- d) in non-slow release tablets or capsules containing more than 500 mg paracetamol;
- e) in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol;
- f) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules except in Schedule 2;
- g) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules except when included in Schedule 2;
- h) for injection;
- i) for the treatment of animals.

#### **Schedule 3**

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

## Schedule 2

PARACETAMOL for therapeutic use:

- a) 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
- b) in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or
- c) 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
- d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or
- e) 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
- f) 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 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 of 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 20 tablets or capsules,
    - (C) compliant 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.

## Appendix F, Part 3

Warning Statements: **97** (Adults: Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor.); and/or **98** (Children and adolescents: Keep to the recommended dose. Don't give this medicine for longer than 48 hours at

a time unless advised to by a doctor.); **99** (If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage); **100** (Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.).

## **Appendix H**

PARACETAMOL.

### **Index**

#### **PARACETAMOL**

cross reference: ASPIRIN, IBUPROFEN, METOCLOPRAMIDE, SALICYLAMIDE, CAFFEINE

Schedule 4

Schedule 3

Schedule 2

Appendix F, Part 3

Appendix H

Paracetamol is also included in Part 2 of the Poisons Standard as follows:

#### **Part 2 – Control on medicines and poisons, section 2.4 – child-resistant closures**

Paracetamol included in Schedule 4, when packed and labelled for the treatment of animals

Nominal capacity: All sizes

#### *Scheduling history*

At the February 1977 and May 1977 meetings of the Poisons Scheduling Committee (PSC), consideration was given to a report from the Analgesics Working Party which had been convened by the Medicines Advisory Committee to determine whether specific analgesics, including paracetamol, should be restricted in their availability and if so, by what means. The Committee also considered whether paracetamol and other analgesics and their derivatives should be available over the counter (OTC) when supplied as a single substance only with pack size restrictions and supplied in strip packs or in containers with suitable child resistant closures. The Committee agreed that a new Schedule 2 entry be created for paracetamol:

- In tablets or capsules each containing 500 milligrams or less of paracetamol as the only therapeutically active constituent;
- The tablets or capsules supplied in blister or strip packaging or in containers with suitable child resistant closures; and
- In a primary pack containing not more than 20 such tablets or capsules; or
- In individually wrapped powders each containing 250 milligrams or less of paracetamol as the only therapeutically active constituent provided such individually wrapped powders were packed in a primary pack containing not more than 10 such powders.

In November 1978, the PSC considered a request that warning statements should appear on scheduled and unscheduled analgesics including paracetamol. The Committee agreed that the following warning statements for paracetamol, aspirin and salicylamide be adopted:

*'WARNING – THIS MEDICATION MAY BE DANGEROUS WHEN USED IN LARGE AMOUNTS OR FOR A LONG PERIOD'*

*or*

*'CAUTION – THIS PREPARATION IS FOR THE RELIEF OF MINOR AND TEMPORARY AILMENTS AND SHOULD BE USED STRICTLY AS DIRECTED. PROLONGED USE WITHOUT MEDICAL SUPERVISION COULD BE HARMFUL.'*

In May 1979, the PSC considered advice regarding inconsistencies relating to the dose and quantity paracetamol, aspirin and salicylamide present in powders and tablets available over the counter. This was based on the premise that the public had a misunderstanding that one powder sachet was the therapeutic equivalent to two tablets. The PSC agreed that the case was reasonable and recommended that the quantity of paracetamol in individually wrapped powders available in Schedule 2 be increased from 250 mg to 1000 mg.

In May 1981, the PSC considered requests to review the existing Schedule 2 entries for the powder form of analgesics, including paracetamol, to allow the use of effervescent dose forms; to reduce the net content of each dose; and to increase the number of doses per pack from 12 to 24. The PSC agreed that while alternative formulations were acceptable, increasing the number of doses per pack (decreased contents notwithstanding) was seen as contrary to the spirit of previous recommendations designed to discourage excessive analgesic consumption.

In February 1989, the National Drugs and Poisons Schedule Committee (NDPSC) were made aware of a new paediatric flavoured 80 mg paracetamol tablet being sold as an unscheduled item through non-pharmacy retail outlets. As a result, the NDPSC considered the unrestricted promotion of unscheduled flavoured paediatric paracetamol tablets. The NDPSC made a foreshadowed recommendation to include paediatric flavoured dose forms of paracetamol in Schedule 2. The foreshadowed recommendation was confirmed at the November 1989 meeting.

In August 1993, the NDPSC gave consideration to the Schedule 2 paracetamol entry which prevented the marketing of any industrial product containing paracetamol, even at very low concentrations. The NDPSC amended the Schedule 2 entry for paracetamol to include the words '*for therapeutic use*'.

In May 1998, the NDPSC considered a request to make paracetamol a Pharmacy Only medicine due to problems with overdoses. The NPPSC agreed that restricting paracetamol to pharmacies would have no substantial effect on deliberate paracetamol poisonings and the scheduling of OTC paracetamol remained unchanged.

In May 2001, the NDPSC considered an application to vary the dose limit for paracetamol in Schedule 2 to exempt a modified release paracetamol product containing 665 mg paracetamol per caplet with 18 caplets per pack. Whilst the NDPSC recognised that sustained release paracetamol may have an advantage over immediate release preparations in terms of reduced dosing frequency, they were concerned that the changed dosage regime, combined with the pharmacokinetics of the new formulation, would lead to an increase in overdose with paracetamol. The NDPSC was of the view that there was a need to assess the safety-in-use for the new dosing regimen and in the treatment of pain in chronic conditions such as osteoarthritis, given the pharmacokinetic profile of sustained release paracetamol and the shift in demographic from the healthy volunteers to an older age group. Consequently, the NDPSC did not agree to vary the Schedule 2 exemption of 500 mg paracetamol limit.

In October 2003, the NDPSC considered the Medicines Evaluation Committee's (MEC) package of warning statements for over the counter paracetamol and subsequent inclusion of paracetamol in Appendix F of the Poisons Standard. The NDPSC agreed to this proposal and the consequential amendments to the Schedule 2 entry for paracetamol. It was also agreed that the effective date would be 1 May 2005.

In October 2006, the NDPSC considered a recommendation arising from the June 2006 Medicines Classification Committee (MCC) meeting with respect to harmonising the Schedule 2 entry for paracetamol with New Zealand. The NDPSC considered the requirement for Schedule 2 (Pharmacy Only) tablets or capsules containing over 500 mg and up to 665 mg of paracetamol to be in slow release form only. After discussion of the request and the reasons behind it, the NDPSC agreed to foreshadow consideration of the scheduling of paracetamol at the February 2007 meeting.

In February 2007, the NDPSC noted the safety concerns surrounding the potential for overdose and toxicity with immediate release doses of paracetamol over 500 mg. With consideration to these safety concerns and in order to harmonise with New Zealand, the NDPSC agreed that slow release paracetamol with >665 mg should remain in Schedule 4 and also agreed to lower the non-slow release cut-off to >500 mg.



In February 2008, the NDPSC considered a proposal to include paracetamol for injection in Schedule 4 of the Poisons Standard. The NDPSC agreed that there were certain circumstances where the use of injectable paracetamol was appropriate and that use of a substance as an injectable required clinical input and supervision. It was agreed that the Schedule 4 entry for paracetamol be amended accordingly.

In May 2012, the ACMS considered a proposal to further restrict the pack size requirements for paracetamol to be exempt from scheduling. The ACMS recommended and the Delegate agreed for Australia to harmonise with New Zealand and restrict the exempt pack size requirements for paracetamol to packs containing 10 g or less of paracetamol. The full reasons for this decision can be found on the [TGA website](#).

In March 2016, the ACMS considered an application to restrict the pack size requirements of paracetamol available in a pharmacy. The Delegate made a final decision to limit the pack size of paracetamol available from a pharmacy to no more than 100 tablets or capsules per pack and no more than 50 wrapped powders or sachets of granules per pack for domestic supply. In addition, bulk pack sizes of paracetamol were specifically limited for supply only to hospitals, nursing homes and pharmacies for dispensing purposes. The full reasons for this decision can be found on the [TGA website](#).

In March 2019, the ACMS and the Joint Advisory Committee on Chemicals and Medicines Scheduling (Joint ACCS-ACMS) considered proposals to amend the Schedule 4 entry for paracetamol with respect to slow release paracetamol and to create a new scheduling entry for a concentrated liquid paracetamol formulation for the animal treatment, respectively. The Delegate's interim decisions, published on the TGA website on 6 June 2019, were to: (i) [replace the words 'slow release' with 'modified release'](#)<sup>53</sup>; and (ii) include [paracetamol for the treatment of animals in Schedule 4](#)<sup>54</sup> of the Poisons Standard. In addition, a new listing will be created in Part 2 – Control on medicines and poisons, section 2.4 – child-resistant closures as follows: 'Paracetamol included in Schedule 4, when packed and labelled for the treatment of animals. Nominal capacity: All sizes'<sup>55</sup>. The final decision was published on the TGA website on 22 August 2019.

#### Australian regulations

- According to the [TGA Database](#),<sup>56</sup> paracetamol is:
  - Available for use as an Active Ingredient in: Biologicals, Export Only, Over the Counter, Prescription medicines;
  - Available for use as an Excipient Ingredient in: Biologicals, Devices, Prescription medicines; and
  - Not available as an Equivalent Ingredient in any application.
- There are 716 medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#)<sup>57</sup> that contain paracetamol as the sole active ingredient or in combination products. Of these 716 products, 49 are oral liquid preparations which include 3 prescription (Schedule 4) and 46 non-prescription medicines (Schedule 2).
- Liquid paracetamol preparations on the ARTG:

Dosage form	Total	Prescription medicines	Non-prescription medicines
Oral liquid	12	1	11

<sup>53</sup> <https://www.tga.gov.au/book-page/15-interim-decision-relation-paracetamol-modified-release>

<sup>54</sup> <https://www.tga.gov.au/book-page/31-interim-decision-relation-paracetamol>

<sup>55</sup> <https://www.tga.gov.au/book-page/31-interim-decision-relation-paracetamol>

<sup>56</sup> <https://www.ebs.tga.gov.au/>

<sup>57</sup> <http://tga-search.clients.funnelback.com/s/search.html?query=&collection=tga-artg>



Oral liquid, solution	19	1	18
Oral liquid, suspension	18	1	17

- Liquid paracetamol products are marketed in formulations containing:
  - 24 mg/mL paracetamol in 50, 100, 200 and 500 mL pack sizes;
  - 48 mg/mL paracetamol in 50, 100, 200 and 500 mL pack sizes;
  - 50 mg/mL paracetamol in 60, 100, 200 and 1000 mL pack sizes;
  - 100 mg/mL paracetamol in 5 and 20 mL pack sizes; and
  - 32.5 mg/mL paracetamol + 1 mg/mL dextromethorphan in 120, 240 and 360 mL pack sizes (intended primarily for use in children, are currently available as a Pharmacy Medicine (Schedule 2)).
- Paracetamol is not permitted to be included in listed medicines as it is not included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No.4 of 2019](#)<sup>58</sup>.
- The [Prescribing medicines in pregnancy database](#)<sup>59</sup> classifies paracetamol as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Paracetamol	A	Central Nervous System	Analgesics and Antipyretics (see also non-steroidal anti-inflammatory agents)	-
<b>Category A</b> – Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.				

- The Medicines Advisory Statement Specification 2019 ([RASML No. 5 – Schedule 1](#))<sup>60</sup> requires the following warning statements pertaining to paracetamol to be included on the labelling. The RASML requirements for paracetamol products are:

Column 1 Substance(s)	Column 2 Conditions	Column 3 Required statements(s)
Paracetamol (Entry 1 of 3)	For the purpose of exclusion from the schedules to the Poisons Standard	<p>Adults: Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised to by a doctor.</p> <p>Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.</p> <p>If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26,</p>

<sup>58</sup> <https://www.legislation.gov.au/Details/F2019L01597>

<sup>59</sup> <https://www.tga.gov.au/prescribing-medicines-pregnancy-database>

<sup>60</sup> <https://www.legislation.gov.au/Details/F2019L00213>

		<p>New Zealand 0800 764 766) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.</p> <p>Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.</p>
Paracetamol (Entry 2 of 3)	In Schedule 2 or 3 to the Poisons Standard	<p>Adults: Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised to by a doctor.</p> <p>and / or</p> <p>Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.</p> <p>If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26, New Zealand 0800 764 766) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.</p> <p>Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.</p>
Paracetamol (Entry 3 of 3)	In combination with ibuprofen, in medicines for oral use	<p>Do not give to children under 12 years of age.</p> <p>Adults: Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised to by a doctor.</p> <p>Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.</p> <p>Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.</p> <p>Do not use if pregnant or trying to become pregnant.</p> <p>Do not use if you have a stomach ulcer.</p> <p>Do not use if you have impaired kidney function.</p> <p>Do not use if you have heart failure.</p> <p>Do not use if you are allergic to ibuprofen or other anti-inflammatory medicines.</p> <p>If you get an allergic reaction, stop taking and see your doctor immediately.</p> <p>Unless a doctor has told you to, do not use if you have asthma.</p> <p>Unless a doctor has told you to, do not use if you are aged 65 years or over.</p> <p>Do not take with other products containing paracetamol, ibuprofen, aspirin or other anti-</p>

		<p>inflammatory medicines or with medicines that you are taking regularly, unless advised to do so by a doctor or pharmacist.</p> <p>If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26, New Zealand 0800 764 766) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.</p>
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- The [Database of Adverse Event Notifications \(DAEN\)](#)<sup>61</sup> contains one hundred and eight (108) reports of adverse events for products containing paracetamol as an active ingredient that are targeted to children, with ninety-nine (99) reports where paracetamol was the single suspected medicine. Of these 99 cases:
  - 9 involved accidental overdose/poisoning;
  - involved the accidental exposure to products by children;
  - involved use of products in unapproved indications/off label use;
  - involved the incorrect dose or administration rate being administered;
  - 1 incorrect drug administration rate;
  - 1 involved hepatotoxicity; and
  - 2 reports of deaths associated with paracetamol use resulting from overdose and sudden infant death syndrome.
- As of 20 June 2019, there are currently no products containing paracetamol listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#).<sup>62</sup>

#### *International regulations*

- Paracetamol is registered with the [European Chemical Agency \(ECHA\)](#)<sup>63</sup> for a variety of uses including pharmaceutical, laboratory and industrial.
- Paracetamol is on the [World Health Organisation's List of Essential Medicines](#),<sup>64</sup> which lists the most effective and safe medicines needed in a health system.
- In Sweden, oral solutions of 24 mg/mL paracetamol are available at non-pharmacy outlets and at pharmacies in 100 mL pack sizes.<sup>65</sup>
- In Ireland, dosage instructions for liquid paracetamol, 120 mg/5mL, were increased in March 2012 from two single bands (3 months to 1 year and 1 year to 6 years) to four separate age bands (3-6 months, 6-24 months, 2-4 years and 4-6 years) with one dose recommended for each age band.<sup>66</sup> Oral liquid paracetamol, 50 mg/mL, is available as a non-pharmacy medicine (60 mL pack size) and a pharmacy medicine (240 mL pack size).<sup>67</sup>
- In the United States (U.S.), acetaminophen (paracetamol) is available in [OTC and prescription medicines](#).<sup>68</sup> On December 22 2011, The U.S. Food and Drug Administration (FDA) informed the public that an additional concentration of liquid acetaminophen marketed for 'infants' (160 mg/5 mL) became available at local stores. Until then, liquid acetaminophen marketed for 'infants' was only available in 80 mg/0.8 mL or 80 mg/mL concentrations. Having two very different

<sup>61</sup> <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

<sup>62</sup> <https://portal.apvma.gov.au/pubcris>

<sup>63</sup> <https://echa.europa.eu/substance-information/-/substanceinfo/100.002.870>

<sup>64</sup> <https://www.who.int/medicines/publications/essentialmedicines/en/>

<sup>65</sup> <https://occup-med.biomedcentral.com/articles/10.1186/s12995-015-0084-3>

<sup>66</sup> [https://www.hpra.ie/docs/default-source/default-document-library/imb\\_pressrelease\\_paracetamolforchildren\\_12march2012.pdf?sfvrsn=0](https://www.hpra.ie/docs/default-source/default-document-library/imb_pressrelease_paracetamolforchildren_12march2012.pdf?sfvrsn=0)

<sup>67</sup> <https://occup-med.biomedcentral.com/articles/10.1186/s12995-015-0084-3/tables/5>

<sup>68</sup> <https://www.fda.gov/drugs/information-drug-class/acetaminophen-information>

concentrations of liquid acetaminophen on the market increased the likelihood for dosing confusion and medication errors involving unintentional overdoses in children. In order to prevent possible dosing confusion between products with different concentrations of acetaminophen, many (but not all) U.S. manufacturers decided to voluntarily change the liquid acetaminophen marketed for infants to make it the same concentration as the product used for older children.<sup>69</sup>

- In the United Kingdom (UK), paracetamol is included on the [General Sales List \(GSL\)](#)<sup>70</sup> and is available in small quantities off the shelf with no pharmacy training required to sell. The largest pack size of paracetamol available in shops without a pharmacist is 16 tablets, but pharmacies can sell packs of 32 tablets. In 2011, new paediatric paracetamol dosing instructions were introduced in the UK. The [UK paediatric paracetamol dosage system](#)<sup>71</sup> has a larger number of narrower age bands and defines a single dose per age band. [Schedule 15 \(Requirements for specific products subject to general sale\) of the UK Human Medicines Regulation 2012](#),<sup>72</sup> restricts liquid paracetamol pack sizes available for general sale to: (i) 160 mL for preparation intended for persons over 12 years of age; and (ii) individual unit doses of not more than 5 mL each, to a maximum of 20 unit doses for preparations intended for persons aged less than 12 years old.
- In New Zealand ([Medicines and Medical Devices Safety Authority \(MEDSAFE\)](#)),<sup>73</sup> paracetamol, depending on its presentation, is available as a Prescription, Restricted (Pharmacist-Only), Pharmacy Only or General Sales medicine. Liquid paracetamol for children and infants over three months is available in two strengths: 120 mg/5 mL and 250 g/5 mL, with individual doses based on body weight. For infants younger than three months or where an infant or child weighs 5 kg or less, a doctor must be seen first.<sup>74</sup>
- In Canada, acetaminophen (paracetamol), when recommended for administration by intravenous injection, is on [Health Canada's Prescription Drug List](#)<sup>75</sup> for human use and veterinary use. It is also available as an OTC medicine and in some presentations is classed as a narcotic under Canada's *Controlled Substances Act (CDSA)*.<sup>76</sup>

#### *Summary of pre-meeting public submissions*

In response to [the notice published under regulation 42ZCZK](#) advising of the proposed amendment, eight (8) submissions were received. One (1) submission requested clarification of the scheduling proposal, two (2) submissions supported the amendment, four (4) submissions opposed the amendment and one (1) submission made comment only.

#### **The main points provided in the submission requesting clarification of the proposed scheduling amendment were:**

- The proposed limits on concentration, total volume and total mass per container do not appear to be mathematically logical or feasible.
- The wording suggests the upper limits in concentration, total volume and total mass per container must all be met (i.e. not exceeded).

#### **The main points provided in support of the proposed amendment were:**

- Paracetamol is the most widely used over-the-counter analgesic agent in the world. It is involved in a large proportion of accidental paediatric exposures and deliberate self-poisonings. Australia should review the current situation of paracetamol availability and work to bring it in line with overseas jurisdictions which have restricted non-pharmacy paracetamol availability (pack sizes

<sup>69</sup> <https://www.fda.gov/drugs/drug-safety-and-availability/questions-and-answers-important-change-concentration-over-counter-otc-liquid-acetaminophen-marketed#q2>

<sup>70</sup> <https://www.nhs.uk/common-health-questions/medicines/what-is-the-law-on-the-sale-of-medicines/>

<sup>71</sup> <https://www.gov.uk/drug-safety-update/paracetamol-updated-dosing-for-children-to-be-introduced>

<sup>72</sup> <http://www.legislation.gov.uk/uksi/2012/1916/schedule/15/made?view=plain>

<sup>73</sup> <https://www.medsafe.govt.nz/profs/class/classintro.asp>

<sup>74</sup> <https://www.kidshealth.org.nz/safe-use-paracetamol-children>

<sup>75</sup> <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/prescription-drug-list/list.html#a2>

<sup>76</sup> <https://laws-lois.justice.gc.ca/eng/acts/c-38.8/>

and/or maximum paracetamol mass). In the UK, reduced pack sizes of paracetamol led to a reduction in deaths resulting from paracetamol overdose<sup>77</sup> and it is relevant to also consider pack sizes of all forms of paracetamol freely available for public purchase.

- It is appropriate to limit the volume or maximum paracetamol mass in Schedule 2 paracetamol liquid preparations, as this will ensure that purchasers of paracetamol liquid preparations will have the benefit of a pharmacist's guidance on appropriate dosage and precautions, provided either directly or under the direction of that pharmacist.
- A product containing large quantities of paracetamol, particularly in liquid form, carries a potential for significant human toxicity (including delayed irreversible hepatotoxicity) if the product is accidentally ingested or deliberately misused. While strongly supporting the introduction of a limit on the amount of paracetamol that can be supplied in the liquid form in Schedule 2, it would be preferable for a limit of 10 g paracetamol per container of liquid preparation in Schedule 2 to be implemented as this is a clearly defined toxic dose in adults. In children the toxic dose is >200mg/kg/24 hours which for a 10 kg child equates to only 2 g.
- Restricting the amount of paracetamol that can be supplied in Schedule 2 to a maximum 10g paracetamol per container of liquid would help to reduce the likelihood of massive paracetamol poisonings from both accidental paediatric exposures and single impulsive purchases, while having minimal impact on access to affordable OTC liquid paracetamol.
- Since January 2014, NSW Poisons Information Centre (PIC) has received in excess of 6800 calls regarding accidental exposures to liquid paracetamol. More than 6220 of these exposures involved children under the age of 5 years. Of these calls 1828 patients were either in or referred to hospital and 1629 of these patients were under the age of 5 years. Hospital referral was due to concerns a toxic dose of paracetamol may have been ingested by the child. 200 mL bottles of paracetamol were much more likely to be implicated in hospital referrals compared with 100ml or smaller bottles.
- In a sample period of calls (23-06-2018 to 02-09-2019) NSW PIC received 684 calls regarding accidental exposures to liquid paracetamol of which 642 calls involved children under the age of 5 years. 205 patients were either in or referred to hospital during this period due to concerns they had ingested a toxic dose of paracetamol and 196 (95.6%) of these patients were under the age of 5 years.
- There is growing evidence from multiple sources that the rate of deliberate self-harm, including deliberate self-poisoning, is increasing amongst young people<sup>78, 79, 80</sup> and that this behaviour is starting at a younger age. In 2018, NSW PIC received 239 calls regarding deliberate self-poisoning with paracetamol in children aged 14 years and under. In 2019 up until mid-September, NSW PIC received 155 calls regarding deliberate self-poisoning with paracetamol in children aged 14 years and under. While most self-poisonings involved paracetamol in tablet form, the concern is that liquid paracetamol may become an increasingly popular self-harm option for younger people due to the relevant ease of ingestion of liquid formulations.

**The main points provided in opposition to the proposed amendment were:**

- The wording of the amendment as proposed is confusing and unclear and appears to contain a mathematical error that will have a significant but unnecessary impact on existing liquid paracetamol products currently available in Schedule 2. It would remove from Schedule 2 and force into Schedule 4, all 100 mg/L 'infant drops' products, all pack sizes greater than 100 mL and the combination product (paracetamol plus dextromethorphan), which cannot meet the TGA proposal.

<sup>77</sup> Hawton, K., Bergen, H., Simkin, S., Dodd, S., Pocock, P., Bernal, W., Gunnell, D., Kapur, N. (2013) long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: Interrupted time series analyses. *British Medical Journal*, 346(7895), 1-9. <http://doi.org/10.1136/bmj.f403>

<sup>78</sup> Perera, J., Wand, T., Bein, K.J., Chalkley, D., Ivers, R., Steinbeck, K.S., et al. Presentations to NSW emergency departments with self-harm, suicidal ideation or intentional poisoning, 2010-2014. *Med. J. Aust.* 2018; 208(8):348-53.

<sup>79</sup> Hiscock, H., Neely, R.J., Lei, S., Freed, G. Paediatric mental and physical health presentations to emergency departments, Victoria, 2008-15. *Med. J. Aust.* 2018; 208(8) 343-8

<sup>80</sup> Hiscock, H., Neely, R.J., Lei, S., Freed, G. Paediatric mental and physical health presentations to emergency departments, Victoria, 2008-15. *Med. J. Aust.* 2018; 208(8) 343-8

- While not in principle opposed to setting a limit on the total amount (volume) of paracetamol that is available per container of liquid preparations to bring them in line with solid dose formulations, no meaningful, evidence-based public health rationale has been presented to support removal of any of these products from the market through re-scheduling. Further, practical issues supporting the need for age-appropriate dose volumes should be considered before any changes are made to the currently available dosage strengths.
- The proposal is inconsistent with both the paracetamol N2 OTC risk categorisation (N1 and N2 classifications are deemed to pose negligible risk) and the Australian Regulatory Guidelines for over the counter medicines (ARGOM) documents issued by the TGA. Liquid paracetamol preparations at dose strengths of 24 mg/mL, 48 mg/mL and 100 mg/mL are permitted under the N2 classification while the ARGOM allows sponsors to supply any of the following strengths of liquid preparations of paracetamol without the need for justification: 24 mg/mL, 48 mg/mL, 50 mg/mL and 100 mg/mL. Deviation from these strengths requires justification.
- Analysis of the DAEN database (1971-2019) corroborates the published data, with only 4 cases of overdose and 8 cases of accidental overdose reported in the last 48 years. Clearly existing measures – the mandatory child-resistant closures, detailed dosing instructions for all ages, clear labelling design, and accurate, age-appropriate measuring devices – are an effective means of protecting Australian consumers.
- While supportive of amendments to the Poisons Standard that would limit the pack size of paracetamol liquid within Schedule 2, the proposed amendment could lead to unintended consequences by limiting pack sizes and strengths available within pharmacies or for general sale. It is suggested that a 5 g maximum per container of liquid paracetamol is appropriate for Schedule 2. Inclusion of larger pack sizes (e.g. up to 25 g paracetamol) in Schedule 3 would allow for continued access to larger volume pack sizes by adult consumers with swallowing difficulties whom rely on liquid medicine formulations.
- It is suggested that a 5 g maximum per container of liquid paracetamol is appropriate for Schedule 2. Inclusion of larger pack sizes (e.g. up to 25 g paracetamol) in Schedule 3 would allow for continued access to larger volume pack sizes by adult consumers with swallowing difficulties whom rely on liquid medicine formulations.
- Dose volume is an important aspect of the acceptability of paediatric liquid preparations. Recognising that *'High-dose volumes pose a risk of incomplete ingestion and, thus, underdosage,'* the WHO recommends *'Efforts should, therefore, be made during pharmaceutical development to minimize the dose volume while recognizing the need to ensure accurate measurements of the dose over the anticipated range'*.<sup>81</sup> Concerns around dose volume and dosing accuracy have been mitigated with the currently available range of liquid paracetamol age-specific dose strengths and corresponding age-appropriate dosing devices available in Australia. It is questionable whether eliminating 11 of the 17 of the currently available liquid paracetamol dose/pack size permutations and forcing consumers to purchase pack sizes that are not age-appropriate or do not contain an age-appropriate dosing device has any tangible value in mitigating the risk of harm from these products.
- There is a potential for paracetamol to be misused, but this is often inadvertent rather than intentional especially with liquid presentations used for children. As noted in the NPS MedicinesWise article on the *'Safe and appropriate use of paracetamol: closing the consumer knowledge gap'*,<sup>82</sup> knowledge gaps in carers of young children may contribute to unintentional misuse and overdose of paracetamol. In a cross-sectional study performed in the USA, only 38% of participants correctly selected and measured the appropriate paracetamol dose for infants or children. Knowledge gaps with respect to paracetamol use in children included:
  - the perception that paracetamol is a safe medicine;
  - an uncertainty around appropriate indications;

<sup>81</sup> <http://apps.who.int/medicinedocs/en/m/abstract/Is19833en/>

<sup>82</sup> <https://www.nps.org.au/news/safe-and-appropriate-use-of-paracetamol-closing-the-consumer-knowledge-gap#r18>



- a lack of awareness of strengths and formulations; and
- the methods used to measure the correct dose.
- If the intent of the proposal is to correct omission of liquids in the Schedule 2 paracetamol entry by specifying an upper limit to the total dose of paracetamol available in liquid preparations, this can be achieved by revising the wording of the proposed amendment to Schedule 2 to read as follows: '*Liquid preparations for oral use containing ~~no greater than 50mg per mL or paracetamol in 100 mL with~~ a maximum of 50 g paracetamol per container*'. Of the three numerical requirements in the proposal, only a 50 g total cut-off would permit the existing products to continue as Schedule 2. Any other upper limit apart from 50 g would need to be justified in terms of the need for the limit and the scientific basis for the limit chosen.

**The main points of the submission that made comment only were:**

- Under 'Reasons for Proposal', the available paracetamol liquid preparations are listed, including: '32.5 mg/mL paracetamol + 1 mg/mL dextromethorphan... (intended primarily for use in children, are currently available as a Pharmacy Medicine (Schedule 2))'. For the purposes of accuracy of the public record, XXXX wishes to clarify that it is incorrect to state that this product was 'intended primarily for use in children'. The labelling dosage instructions limits use to adults and children 12 years and over, and also included on the label is the warning statement 'Do not use this product in children under 12 years of age'.

*Summary of ACMS advice/recommendations to the Delegate*

The Committee recommended that the current Schedule 3 and Schedule 2 entries for paracetamol be amended in the Poisons Standard as follows:

**Schedule 3 – Amend Entry\***

PARACETAMOL:

- when combined with ibuprofen in a primary pack containing 30 dosage units or less except when included in Schedule 2; or
- in modified release tablets or capsules containing 665 mg or less paracetamol; or
- in liquid preparations for oral use **except** when in Schedule 2.

\*The proposed amended Schedule 3 entry for paracetamol as written includes the [final decision](#)<sup>83</sup> for modified paracetamol that will be implemented 1 June 2020.

**Schedule 2 – Amend Entry**

PARACETAMOL for therapeutic use:

- in liquid preparations for oral use containing a maximum of 10 g of paracetamol per container;
- 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
- in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or
- 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
- in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or

<sup>83</sup> <https://www.tga.gov.au/book-page/14-final-decision-relation-paracetamol-modified-release>



- 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 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 of 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 20 tablets or capsules,
    - (C) compliant 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.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) the risks and benefits of the use of a substance; (b) the purpose 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 that the Secretary considers necessary to protect public health.

The reasons for the advice included:

52E(1) Considerations	Reasons
a – the risks and benefits of the use of a substance	<p><i>Risks:</i></p> <ul style="list-style-type: none"> <li>The risks of paracetamol are well known. Paracetamol is involved in deliberate self-poisoning and is the single most commonly used drug in overdoses leading to hospital presentations. Risks from overdose – either deliberate or accidental – can include severe and life threatening hepatotoxicity.</li> </ul> <p><i>Benefits:</i></p> <ul style="list-style-type: none"> <li>Paracetamol has an established safety profile at therapeutic doses and it is widely used in the community.</li> </ul>

	<ul style="list-style-type: none"> <li>When used according to label instructions and for short duration, paracetamol has analgesic properties and provides relief of mild to moderate pain.</li> <li>Paracetamol is generally first line therapy used in the community.</li> </ul>
b – the purposes for which a substance is to be used and the extent of use of a substance	<ul style="list-style-type: none"> <li>Analgesia and used for fever</li> </ul>
c – the toxicity of a substance	<ul style="list-style-type: none"> <li>Well established safety and toxicity profile. Toxicity is dose and patient weight dependent</li> </ul>
d – the dosage, formulation, labelling, packaging and presentation of a substance	<ul style="list-style-type: none"> <li>Paracetamol is currently available in tablet and liquid formulations.</li> </ul>
e – the potential for abuse of a substance	<ul style="list-style-type: none"> <li>Not applicable for single ingredient paracetamol preparations.</li> <li>Paracetamol is the most commonly taken drug in overdose.</li> </ul>
f – any other matters that the Secretary considers necessary to protect public health	<ul style="list-style-type: none"> <li>Liquid paracetamol has not previously had an upper limit in any schedule entry in the Poisons Standard.</li> </ul>

#### *Delegate's considerations*

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to paracetamol;
- Advisory Committee on Medicines Scheduling's advice;
- The public submissions received by the [first closing date](#);
- Section 52E of the *Therapeutic Goods Act 1989*, in particular (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (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 that the Secretary considers necessary to protect public health;
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- [Scheduling Handbook](#) (V 1.1, July 2019).

#### *Reasons for the interim decision*

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and 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 that the Secretary considers necessary to protect public health.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the Scheduling Factors for Schedule 2 and 3.

I have made an interim decision to amend the Schedule 2 and 3 entries of paracetamol in the Poisons Standard and I have set out my reasons below.

Liquid paracetamol is available in different strengths and formulations (including baby drops, elixirs and suspensions) that are intended for use in babies, infants, children and adults for the temporary relief of pain and fever. Liquid formulations containing paracetamol at 24, 48, 50 and 100 mg/mL, which are intended primarily for use in children, are currently available as Pharmacy Medicines (Schedule 2). In March 2019, the Joint ACCS-ACMS #21 considered a proposal to amend the Poisons Standard with respect to paracetamol for animal use. Separate to this discussion, it was proposed that the Schedule 2 entry for paracetamol should be amended to restrict the volume of liquid paracetamol available for human use. In the [interim decision](#)<sup>84</sup> published on the TGA website on 6 June 2019, the Delegate at that time stated that, *'In relation to the separate matter of paracetamol for human use, a future delegate initiated application was appropriate to restrict the volume of liquid paracetamol available for human use in Schedule 2.'*

At present, there is no limit on the amount of paracetamol that can be supplied in the liquid form in Schedule 2. While the therapeutic doses of paracetamol are considered safe, unintentional and intentional exposure to high doses results in severe toxic effects. Paracetamol overdose is the leading cause of paediatric acute liver failure in Australia and New Zealand with affected children receiving excess paracetamol for a variety of reasons, including too frequent administration, co-administration with other medicines containing paracetamol and prolonged administration of regular paracetamol doses (for a period of up to 24 days).<sup>85</sup>

I note that there is a high prevalence of accidental paracetamol poisoning in the community, in both adults and children. Data from the NSW PIC shows a considerable number of calls have been received regarding accidental exposures to liquid paracetamol since 2014. However, while a product containing large quantities of paracetamol, particularly in liquid form, may carry potential for significant human toxicity if the product is accidentally ingested or deliberately misused, there is no clear evidence that the size of the bottle is contributing to the risks of harm. Further, I have seen no clear evidence that liquid paracetamol has been used for self-harm, with most evidence of harm relating to paracetamol in tablet preparations.

Paracetamol is one of the most commonly used OTC analgesic which is perceived as a safe medicine by consumers. While paracetamol has well established safety and toxicity profiles, it can have a narrow safety margin. Therefore, I am of the view that it is appropriate to restrict liquid paracetamol preparations available under Schedule 2. Even though there is presently no meaningful, evidence-based public health rationale to support such a restriction, comments received in response to the pre-meeting public consultation, gave in principle support provided any scheduling changes did not restrict access to existing pack sizes and strengths currently available within pharmacies or for general sale. I note the ambiguity in the scheduling amendment as proposed which included both a concentration cut-off (50 mg/mL) and two different weight cut-offs (5 g and 50 g). Given the lack of evidence of harm as previously discussed, I do not support a concentration cut-off. A concentration cut-off will do nothing to limit current pack size availability and would remove infant drop preparations from Schedule 2 sale. I have decided therefore to limit the total amount of paracetamol that is available per container of liquid paracetamol.

Based on the maximum toxic dose of paracetamol for adults (toxic dose in adults equates to 10 g paracetamol), a 10 g paracetamol weight limit per pack would be consistent with international standards and would remove the 500 mL paediatric formulation pack size and 1000 mL adult formulation pack size from Schedule 2. Whilst this weight limit is unlikely to have a significant impact on paediatric poisonings which can occur at 2 g, it has the potential to reduce the likelihood of significant paracetamol poisonings from both accidental paediatric exposures and single impulsive purchases, while having minimal impact on access to affordable over the counter (OTC) liquid paracetamol preparations. Furthermore, a maximum of 10 g of paracetamol per container in Schedule 2 would not limit access to essential medicines for families that use the 200 mL bottles and will ensure continued access to larger quantities for adults with genuine needs for liquid preparations (e.g. adults who cannot swallow tablets).

<sup>84</sup> <https://www.tga.gov.au/book-page/31-interim-decision-relation-paracetamol>

<sup>85</sup> Rajanayagam J, Bishop JR, Lewindon PJ, *et al.*, Paracetamol-associated acute liver failure in Australian and New Zealand children: high rate of medication errors. Arch Dis Child (2015) 100:77-80.

Paracetamol is used widely in the community for children, has a favourable risk and safety profile when used within recommended doses and is often used as a first-line therapy. However, there is a potential for paracetamol to be misused, but this is often inadvertent rather than intentional especially with liquid presentations used for children. As noted in the NPS MedicinesWise article on the '*Safe and appropriate use of paracetamol: closing the consumer knowledge gap*',<sup>86</sup> knowledge gaps in carers of young children may contribute to unintentional misuse and overdose of paracetamol. Two important aspects which impact the safe use of liquid paracetamol paediatric preparations are dose volume and dose accuracy. Concerns around dose volume and dosing accuracy have been mitigated with the currently available range of liquid paracetamol age-specific dose strengths and corresponding age-appropriate dosing devices available in Australia. Implementation of a 10 g paracetamol weight limit per pack will minimise the impact on these currently available paediatric liquid preparations ensuring care-givers will continue to have readily available access to these age-appropriate treatment options while still ensuring that a reasonable maximum limit is set for the availability of liquid paracetamol under Schedule 2 in order to minimise risks to public health. While no clear evidence has been presented that bottle size is a contributing factor in paracetamol poisoning, a product containing large quantities of paracetamol, particularly in liquid form, may carry potential for significant human toxicity if the product is accidentally ingested or deliberately misused. However, I am satisfied that potential risks associated with preparations containing greater than 10 g paracetamol per pack can be adequately controlled through pharmacist counselling via a Schedule 3 listing unless otherwise scheduled (e.g. for veterinary use).

The Scheduling Policy Framework aims to facilitate access to medicines and other chemicals while minimising risk to public health. In view of the known risks of paracetamol toxicity to humans (the acute toxic effects include hepatic necrosis and renal tubular necrosis), and in the interests of public health, it is appropriate to limit the amount of paracetamol in Schedule 2 paracetamol liquid preparations to 10 g, with preparations above 10 g of paracetamol included in Schedule 3.

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<sup>86</sup> <https://www.nps.org.au/news/safe-and-appropriate-use-of-paracetamol-closing-the-consumer-knowledge-gap#r18>

## 1.5. Interim decision in relation to Paracetamol + ibuprofen

### Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision not to amend the current Poisons Standard in relation to paracetamol (in combination with ibuprofen).

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

##### *Applicant's scheduling proposal and reasons for the proposal*

An application to amend the Schedule 2, Schedule 3 and Schedule 4 entries for paracetamol when in combination with paracetamol was considered.

The Applicant's proposed amendments to the Poisons Standard were:

#### **Schedule 4 – Amend Entry**

##### **PARACETAMOL:**

- a) when combined with aspirin or salicylamide or any derivative of these substances except when separately specified in these Schedules;
- b) when combined with ibuprofen in a primary pack containing more than 3050 dosage units;
- c) in slow release tablets or capsules containing more than 665 mg paracetamol;
- d) in non-slow release tablets or capsules containing more than 500 mg paracetamol;
- e) in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol;
- f) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules except in schedule 2;
- g) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules except when included in Schedule 2;
- h) for injection;
- i) for the treatment of animals.

#### **Schedule 3 – Amend Entry**

PARACETAMOL when combined with ibuprofen in a primary pack containing ~~30~~50 dosage units or less **except** when included in **or expressly excluded from** Schedule 2.

#### **Schedule 2 – Amend Entry**

##### **PARACETAMOL for therapeutic use:**

- a) 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 1230 dosage units per pack except 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
- b) in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or
- c) 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

- d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or
- e) 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
- f) 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 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 of age or less, and
    - (D) not labelled for the treatment of children under 12 years of age when combined with 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 20 tablets or capsules,
    - (C) compliant 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.

## **Appendix F, Part 3**

### **PARACETAMOL**

Warning Statements: **97** (Adults: Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor); AND/OR **98** (Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor); **99** (If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage); **100** (Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist).

## **Appendix H**

### **PARACETAMOL.**

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### **PARACETAMOL**

cross reference: ASPIRIN, IBUPROFEN, METOCLOPRAMIDE, SALICYLAMIDE, CAFFEINE



Schedule 4  
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The Applicant's main points provided in support of the proposed amendments were as follows:

- This application proposes a logical sequence of controls on paracetamol/ibuprofen combinations based on pack size with 12 dosage units or less as 'exempted from scheduling', 13 to 30 dosage units or less as 'Pharmacy Medicine' (Schedule 2), 31 to 50 dosage units or less as 'Pharmacist Only Medicine' (Schedule 3) and larger pack sizes as 'Prescription medicine' (Schedule 4).
- Paracetamol and ibuprofen used separately have long been recognised as safe and effective for the treatment of simple self-limiting pain. The risks that do exist are addressed by label warning statements with small packs being available for general sale and larger packs being available in Schedules 2 or 3.
- The proposed pack sizes for the combination in terms of days' treatment per pack are broadly consistent with pack sizes currently available without prescription for paracetamol or ibuprofen used separately. Quantities of up to 17 days' supply may legitimately be required for short term treatment of intermittent pain over a period of time or where more than one person in a household uses the same medicine. This is currently the case for ibuprofen in Schedule 2 and is now being proposed for the combination in Schedule 3 where pharmacist advice represents a further level of safety.
- The two 'originator' products approved by TGA (XXXXXXXXXXXXXX) have now been available in Australia since 2013/2014 and in New Zealand since 2011. During that time there have been no 'serious' adverse events reported to TGA or to Medsafe and the number of adverse reactions relative to sales has been small.
- In New Zealand XXXXXXXXXXXXXXXX have been available since 2011 as 'general sales' items in packs of 20 and as 'pharmacy medicine' items in packs of 100. In addition, the maximum daily dose of XXXXXX in Australia is less than half the maximum daily dose of XXXXXX and exactly half the maximum daily dose of XXXXXX in New Zealand.
- It has been accepted that the risk of consumers confusing their temporary pain condition with more serious diseases or conditions is very small.
- In recognition of the differences in approved dose between the two major brands of paracetamol/ibuprofen (XXXXXXXXXXXXXX) and between these products and paracetamol and ibuprofen used separately XXXXXXXX proposes to draw attention to the '1 tablet dose' of XXXXX on the front of pack.
- Combinations of paracetamol and ibuprofen are able to be supplied in pack sizes of up to 12 dosage units, with reasonable safety, without access to health professional advice and this small pack size falls outside the factors for Schedules 2, 3, 4 or 8 in the same way that small packs of paracetamol or ibuprofen used separately fall outside these factors.
- Ongoing long-term treatment with any analgesic requires medical intervention. The proposed Schedule 4 pack of more than 50 dosage units will achieve this while enabling medical practitioners to prescribe larger quantities when appropriate.

#### *Current scheduling status*

##### *Paracetamol*

Paracetamol is currently listed in Schedules 2, 3 and 4 and Appendix F and H of the Poisons Standard 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;



- b) when combined with ibuprofen in a primary pack containing more than 30 dosage units;
- c) in slow release tablets or capsules containing more than 665 mg paracetamol;
- d) in non-slow release tablets or capsules containing more than 500 mg paracetamol;
- e) in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol;
- f) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules except in Schedule 2;
- g) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules except when included in Schedule 2;
- h) for injection;
- i) for the treatment of animals.

### **Schedule 3**

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

### **Schedule 2**

PARACETAMOL for therapeutic use:

- a) 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
- b) in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or
- c) 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
- d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or
- e) 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
- f) 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 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 of 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 20 tablets or capsules,
  - (C) compliant 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.

### **Appendix F, Part 3**

Warning Statements: **97** (Adults: Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor.); and/or **98** (Children and adolescents: Keep to the recommended dose. Don't give this medicine for longer than 48 hours at a time unless advised to by a doctor.); **99** (If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage); **100** (Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.)

### **Appendix H**

PARACETAMOL.

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#### **PARACETAMOL**

cross reference: ASPIRIN, IBUPROFEN, METOCLOPRAMIDE, SALICYLAMIDE, CAFFEINE

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Paracetamol is also included in Part 2 of the Poisons Standard as follows:

#### **Part 2 – Control on medicines and poisons, section 2.4 – child-resistant closures**

Paracetamol included in Schedule 4, when packed and labelled for the treatment of animals

Nominal capacity: All sizes

#### *Ibuprofen*

Ibuprofen is listed in Schedules 2, 3 and 4 and Appendix F and H of the Poisons Standard as follows:

#### **Schedule 4**

IBUPROFEN **except:**

- a) when included in or expressly excluded from Schedule 2 or 3; or
- b) in preparations for dermal use.

### Schedule 3

#### IBUPROFEN:

- a) in divided preparations, each containing 400 mg or less of ibuprofen in a primary pack containing not more than 50 dosage units, when labelled:
  - i) with a recommended daily dose of 1200 mg or less of ibuprofen; and
  - ii) not for the treatment of children under 12 years of age; or
- b) in a modified release dosage form, each containing 600 mg of ibuprofen in a primary pack containing not more than 32 dosage units, when labelled:
  - i) with a recommended daily dose of 1200 mg or less of ibuprofen; and
  - ii) not for the treatment of children under 12 years of age;

**except** when included in or expressly excluded from Schedule 2.

### Schedule 2

IBUPROFEN in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen:

- a) in liquid preparations when sold in the manufacturer's original pack containing 8 g or less of ibuprofen; or
- b) in divided preparations, each containing 200 mg or less of ibuprofen, in packs of not more than 100 dosage units **except** when:
  - i) as the only therapeutically active constituent (other than phenylephrine or when combined with an effervescent agent);
  - ii) packed in blister or strip packaging or in a container with a child-resistant closure;
  - iii) in a primary pack containing not more than 25 dosage units;
  - iv) compliant with the requirements of the Required Advisory Statements for Medicine Labels;
  - v) not labelled for the treatment of children 6 years of age or less; and
  - vi) not labelled for the treatment of children under 12 years of age when combined with phenylephrine.

### Appendix F, Part 3

#### IBUPROFEN

##### Warning Statements:

**101:** Don't use [this product/name of the product]:

If you have a stomach ulcer.

In the last 3 months of pregnancy. [This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea.]

If you are allergic to (name of substance) or anti-inflammatory medicines

**104:** Unless a doctor has told you to, don't use [*this product/name of the product*]:

For more than a few days at a time.

With other medicines containing (name of substance) or other anti-inflammatory medicines.

If you have asthma.

If you are pregnant. [This statement may be omitted in preparations used exclusively for the treatment of dysmenorrhoea.]

## **Appendix H**

IBUPROFEN.

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### **IBUPROFEN**

cross reference: PARACETAMOL

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### *Scheduling history*

#### *Paracetamol/ibuprofen combinations*

In June 2010, the NDPSC considered the scheduling of a combination of ibuprofen and paracetamol and agreed that the current scheduling remained appropriate – Schedule 2 for combinations of up to 200 mg ibuprofen and 500 mg paracetamol in packs of up to 100 dosage units.

In February 2011, the Advisory Committee on Medicines Scheduling (ACMS) considered a proposal from the Advisory Committee on Non-Prescription Medicines (ACNM) that the Delegate/ACMS consider up-scheduling paracetamol/ibuprofen combinations (containing up to 500 mg paracetamol/200 mg ibuprofen) from Schedule 2 to Schedule 3. The ACNM had also recommended consideration of a maximum pack size for Schedule 3 paracetamol/ibuprofen combinations. The ACNM, in an assessment of an application to register a combination paracetamol/ibuprofen product, had raised concerns that the sponsor had not satisfactorily established the safety of the product, and considered that pharmacist intervention was needed to assist consumers with safe use of the combination. The ACMS recommended that the combination paracetamol/ibuprofen products that were in Schedule 2 should be rescheduled to Schedule 3, when in packs containing 30 dosage units or less, with larger packs to be included in Schedule 4. The Delegate agreed with the ACMS advice and in September 2011, the Poisons Standard was amended to move paracetamol combined with ibuprofen to Schedule 3 in pack sizes of 30 units or less and Schedule 4 (all other products).

In October 2012, the ACMS considered proposals to reschedule paracetamol 500 mg when combined with ibuprofen 200 mg from Schedule 3 to Schedule 2 in packs containing 12 dosage units or less and to also include Schedule 3 paracetamol when combined with ibuprofen in Appendix H. The ACMS recommended that the current scheduling of paracetamol in combination with ibuprofen remained appropriate, and that paracetamol in combination with ibuprofen should not be included in Appendix H. The reasons for opposing rescheduling to Schedule 2 included insufficient data to disprove the safety concerns with the combination, lack of evidence to support rescheduling, lack of long-term evidence of safety of the combination, potential for additive gastrointestinal side effects, potential for inadvertent misuse and no experience with use of paracetamol/ibuprofen combination products in Australia. The ACMS also considered that there were no public health benefits with inclusion of the combination in Appendix H, and that advertising could lead to inappropriate use. The Delegate agreed with the Committee's advice.

In March 2015, the ACMS considered a proposal to create a new entry for paracetamol/ibuprofen in Appendix H. The ACMS recommended that the current scheduling of paracetamol when combined with ibuprofen remained appropriate. The ACMS considered that the public health risk from advertising would be seen as first line therapy and that there was little evidence to support the applicant claim that an Appendix H entry would transfer demand from codeine combination analgesics to non-codeine combination analgesics. The Delegate agreed with the Committee's advice.

In November 2015, the ACMS considered a proposal to amend the Schedule 2 entry for paracetamol to include paracetamol when combined with ibuprofen in pack sizes of 12 dosage units or less. The ACMS supported the proposal on the basis of the well-established safety profile, low risk of diversion/abuse/addiction and that the medicine provides an effective option for short term use for moderate pain. Following an interim decision in alignment with committee advice and subsequent consideration of the submissions on the interim decision, the Delegate decided to vary the interim decision. In view of the dosage levels of paracetamol and ibuprofen, the Delegate considered it is more appropriate to limit the Schedule 2 entry to 12 dosage units per pack rather than 3 days' supply packs as this would ensure the total paracetamol available in the pack would not be excessive. The implementation date was 1 June 2016.

In July 2017, the ACMS considered a proposal to amend the Schedule 2 entry of paracetamol combined with ibuprofen to increase the pack size from 12 to 24 dosage units or less. The ACMS recommended that the current scheduling of paracetamol when combined with ibuprofen remains appropriate. The ACMS considered the risk of overdosing on ibuprofen combined with paracetamol, the risk of potential adverse effects if the Schedule 2 pack size increase, the reduction in pharmacist advice and the potential for increased delay in consumers seeking advice. The Delegate agreed with the Committee's advice and the scheduling remained unchanged.

In June 2018, the ACMS considered a proposal to amend the Schedule 3 and Schedule 4 entries for paracetamol combined with ibuprofen to increase the dosage units from 30 to 50. The ACMS recommended that the current scheduling of paracetamol when combined with ibuprofen remained appropriate. The Delegate agreed with the Committee's advice and stated in the final decision that increasing the pack size from 10 days' supply (30 tablets) to 17 days' supply (50 tablets) may encourage self-treatment of chronic pain, which is outside the approved acute short term pain indication. The availability of larger quantities of any analgesic increases the likelihood of misadventure. Consumers should only have access to clinically appropriate quantities.

#### *Australian regulations*

##### **Paracetamol combined with ibuprofen**

- There are 24 medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](https://www.tga.gov.au/artg)<sup>87</sup> that contain paracetamol combined with ibuprofen as active ingredients. There is one (1) prescription medicine and 23 non-prescription medicines.
- The Medicines Advisory Statement Specification 2019 ([RASML No. 5 – Schedule 1](https://www.legislation.gov.au/Details/F2019L00213))<sup>88</sup> requires the following warning statements pertaining to paracetamol and ibuprofen to be included on the labelling. The RASML requirements for paracetamol products are:

Substance(s)	Conditions	Required statements(s)
Ibuprofen (Entry 5 of 6)	In combination with paracetamol, in medicines for oral use	<p>Do not give to children under 12 years of age.</p> <p>Adults: Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised to by a doctor.</p> <p>Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.</p> <p>Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.</p> <p>Do not use if pregnant or trying to become pregnant.</p> <p>Do not use if you have a stomach ulcer.</p> <p>Do not use if you have impaired kidney function.</p>

<sup>87</sup> <https://www.tga.gov.au/artg>

<sup>88</sup> <https://www.legislation.gov.au/Details/F2019L00213>

		<p>Do not use if you have heart failure.</p> <p>Do not use if you are allergic to ibuprofen or other anti-inflammatory medicines.</p> <p>If you get an allergic reaction, stop taking and see your doctor immediately.</p> <p>Unless a doctor has told you to, do not use if you have asthma.</p> <p>Unless a doctor has told you to, do not use if you are aged 65 years or over.</p> <p>Do not take with other products containing paracetamol, ibuprofen, aspirin or other anti-inflammatory medicines or with medicines that you are taking regularly, unless advised to do so by a doctor or pharmacist.</p> <p>If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26, New Zealand 0800 764 766) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.</p>
Paracetamol (Entry 3 of 3)	In combination with ibuprofen, in medicines for oral use	<p>Do not give to children under 12 years of age.</p> <p>Adults: Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised to by a doctor.</p> <p>Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.</p> <p>Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.</p> <p>Do not use if pregnant or trying to become pregnant.</p> <p>Do not use if you have a stomach ulcer.</p> <p>Do not use if you have impaired kidney function.</p> <p>Do not use if you have heart failure.</p> <p>Do not use if you are allergic to ibuprofen or other anti-inflammatory medicines.</p> <p>If you get an allergic reaction, stop taking and see your doctor immediately.</p> <p>Unless a doctor has told you to, do not use if you have asthma.</p> <p>Unless a doctor has told you to, do not use if you are aged 65 years or over.</p> <p>Do not take with other products containing paracetamol, ibuprofen, aspirin or other anti-inflammatory medicines or with medicines that you are taking regularly, unless advised to do so by a doctor or pharmacist.</p> <p>If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26, New Zealand 0800 764 766) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.</p>

- There has been one (1) reported case of adverse events related to paracetamol combined with ibuprofen in the [Database of Adverse Event Notifications \(DAEN\)](#),<sup>89</sup> with one (1) report where paracetamol combined with ibuprofen was the single suspected medicine. There were no reports of death associated with paracetamol combined with ibuprofen use.

## Paracetamol

- According to the [TGA Ingredient Database](#),<sup>90</sup> paracetamol is:
  - Available for use as an active ingredient in biologicals, export only, over the counter and prescription medicines;
  - Available for use as an excipient ingredient in biologicals, devices and prescription medicines; and
  - Not available as an equivalent ingredient in any application.
- There are 690 medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#)<sup>91</sup> that contain paracetamol as an active ingredient. These include 138 prescription and 511 non-prescription medicines.
- Paracetamol is not permitted to be included in listed medicines as it is not included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2019](#)<sup>92</sup>.
- The [Prescribing medicines in pregnancy database](#)<sup>93</sup> classifies paracetamol as:

Drug name	Category	Classification Level 1	Classification Level 2
Paracetamol	A	Central Nervous System	Analgesics and Antipyretics (see also non-steroidal anti-inflammatory agents)
<b>Category A</b> – Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.			

- The Medicines Advisory Statement Specification 2019 ([RASML No. 5 – Schedule 1](#))<sup>94</sup> requires the following warning statements pertaining to paracetamol to be included on the labelling. The RASML requirements for paracetamol products are:

Substance(s)	Conditions	Required statements(s)
Paracetamol (Entry 1 of 3)	For the purpose of exclusion from the schedules to the Poisons Standard	<p>Adults: Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised to by a doctor.</p> <p>Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.</p> <p>If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26, New Zealand 0800 764 766) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.</p>

<sup>89</sup> <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

<sup>90</sup> <https://www.ebs.tga.gov.au/>

<sup>91</sup> <https://www.tga.gov.au/artg>

<sup>92</sup> <https://www.legislation.gov.au/Details/F2019L01597>

<sup>93</sup> <https://www.tga.gov.au/prescribing-medicines-pregnancy-database>

<sup>94</sup> <https://www.legislation.gov.au/Details/F2019L00213>



		Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.
Paracetamol (Entry 2 of 3)	In Schedule 2 or 3 to the Poisons Standard	<p>Adults: Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised to by a doctor.</p> <p>and / or</p> <p>Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.</p> <p>If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26, New Zealand 0800 764 766) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.</p> <p>Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.</p>
Paracetamol (Entry 3 of 3)	In combination with ibuprofen, in medicines for oral use	<p>Do not give to children under 12 years of age.</p> <p>Adults: Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised to by a doctor.</p> <p>Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.</p> <p>Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.</p> <p>Do not use if pregnant or trying to become pregnant.</p> <p>Do not use if you have a stomach ulcer.</p> <p>Do not use if you have impaired kidney function.</p> <p>Do not use if you have heart failure.</p> <p>Do not use if you are allergic to ibuprofen or other anti-inflammatory medicines.</p> <p>If you get an allergic reaction, stop taking and see your doctor immediately.</p> <p>Unless a doctor has told you to, do not use if you have asthma.</p> <p>Unless a doctor has told you to, do not use if you are aged 65 years or over.</p> <p>Do not take with other products containing paracetamol, ibuprofen, aspirin or other anti-inflammatory medicines or with medicines that you are taking regularly, unless advised to do so by a doctor or pharmacist.</p> <p>If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26, New Zealand 0800 764 766) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.</p>

- The [Database of Adverse Event Notifications \(DAEN\)](https://apps.tga.gov.au/Prod/daen/daen-entry.aspx)<sup>95</sup> contains 4500 reports of adverse events for products containing paracetamol as an active ingredient, with 2014 reports where paracetamol was the single suspected medicine. There were 203 reports of deaths associated with paracetamol use.
- As of 7 July 2019, there are currently no products containing paracetamol listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](https://portal.apvma.gov.au/pubcris).<sup>96</sup>

## Ibuprofen

- According to the [TGA Ingredient Database](https://www.tga.gov.au/ingredient-database),<sup>97</sup> ibuprofen is:
  - Available for use as an active ingredient in biologicals, export only, over the counter and prescription medicines;
  - Available for use as an excipient ingredient in biologicals, devices and prescription medicines; and
  - Available as an equivalent ingredient in biologicals, export only and prescription medicines.
- There are 240 medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](https://www.tga.gov.au/artg)<sup>98</sup> that contain ibuprofen as an active ingredient. These include 20 prescription and 214 non-prescription medicines.
- Ibuprofen is not permitted to be included in listed medicines as it is not included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2019](https://www.tga.gov.au/therapeutic-goods-permissible-ingredients-determination-no-4-of-2019).<sup>99</sup>
- The [Prescribing medicines in pregnancy database](https://www.tga.gov.au/prescribing-medicines-pregnancy-database)<sup>100</sup> classifies ibuprofen as:

Drug name	Category	Classification Level 1	Classification Level 2	Additional information
Ibuprofen	C	Musculoskeletal System	Non-steroidal anti-inflammatory drugs (NSAIDs)	Non-steroidal anti-inflammatory (NSAIDs) agents inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the foetal ductus arteriosus, foetal renal impairment, inhibition of platelet aggregation, and delay labour and birth. Continuous treatment with NSAIDs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with an inhibitory effect on prostaglandin synthesis should be avoided.
<b>Category C</b> – Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.				

- The [Database of Adverse Event Notifications \(DAEN\)](https://apps.tga.gov.au/Prod/daen/daen-entry.aspx)<sup>101</sup> contains 1751 reports of adverse events for products containing ibuprofen as an active ingredient, with 1188 reports where ibuprofen was the single suspected medicine. There were 56 reports of deaths associated with ibuprofen use.

<sup>95</sup> <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

<sup>96</sup> <https://portal.apvma.gov.au/pubcris>

<sup>97</sup> <https://www.ebs.tga.gov.au/>

<sup>98</sup> <https://www.tga.gov.au/artg>

<sup>99</sup> <https://www.legislation.gov.au/Details/F2019L01597>

<sup>100</sup> <https://www.tga.gov.au/prescribing-medicines-pregnancy-database>

<sup>101</sup> <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

- As of 7 July 2019, there are currently no products containing paracetamol listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](https://portal.apvma.gov.au/pubcris).<sup>102</sup>
- The Medicines Advisory Statement Specification 2019 ([RASML No. 5 – Schedule 1](https://www.legislation.gov.au/Details/F2019L00213))<sup>103</sup> requires the following warning statements pertaining to ibuprofen to be included on the labelling. The RASML requirements for ibuprofen products are:

Substance(s)	Conditions	Required statements(s)
Ibuprofen (Entry 1 of 6)	For the purpose of exclusion from the schedules to the SUSMP, when the preparation is for oral use in adults and children aged 12 years and over.	<p>Do not use if you have a stomach ulcer.</p> <p>Do not use if you have impaired kidney function.</p> <p>Do not use if you have heart failure.</p> <p>Do not use if you are allergic to ibuprofen or other anti-inflammatory medicines.</p> <p>If you get an allergic reaction, stop taking and see your doctor immediately.</p> <p>Unless a doctor has told you to, do not use if you have asthma.</p> <p>Unless advised by your doctor or pharmacist, do not use with products containing ibuprofen, aspirin or other anti-inflammatory medicines or with medicines that you are taking regularly.</p> <p>Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.</p> <p>Do not use if trying to become pregnant, or during the first 6 months of pregnancy, except on doctor's advice. Do not use at all during the last 3 months of pregnancy.</p> <p>Unless a doctor has told you to, do not use if you are aged 65 years or over.</p>
Ibuprofen (Entry 2 of 6)	When included in a schedule to the SUSMP for oral use in adults and children aged 12 years and over	<p>Do not use if you have a stomach ulcer.</p> <p>Do not use if you have impaired kidney function.</p> <p>Do not use if you have heart failure.</p> <p>Do not use if you are allergic to ibuprofen or other anti-inflammatory medicines.</p> <p>If you get an allergic reaction, stop taking and see your doctor immediately.</p> <p>Unless a doctor has told you to, do not use if you have asthma.</p> <p>Unless advised by your doctor or pharmacist, do not use with products containing ibuprofen, aspirin or other anti-inflammatory medicines or with medicines that you are taking regularly.</p> <p>Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful and</p>

<sup>102</sup> <https://portal.apvma.gov.au/pubcris>

<sup>103</sup> <https://www.legislation.gov.au/Details/F2019L00213>

		<p>increase the risk of heart attack, stroke or liver damage.</p> <p>Do not use if trying to become pregnant, or during the first 6 months of pregnancy, except on doctor's advice. Do not use at all during the last 3 months of pregnancy.</p>
<p>Ibuprofen (Entry 3 of 6)</p>	<p>For the purpose of exclusion from the schedules to the SUSMP, for oral use in children under 12 years of age</p>	<p>Do not use if you have a stomach ulcer.</p> <p>Do not use if you have impaired kidney function.</p> <p>Do not use if you have heart failure.</p> <p>Do not use if you are allergic to ibuprofen or other anti-inflammatory medicines.</p> <p>If you get an allergic reaction, stop taking and see your doctor immediately.</p> <p>Unless a doctor has told you to, do not use if you have asthma.</p> <p>Unless advised by your doctor or pharmacist, do not use with products containing ibuprofen, aspirin or other anti-inflammatory medicines or with medicines that you are taking regularly.</p> <p>Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.</p> <p>Do not use if trying to become pregnant, or during the first 6 months of pregnancy, except on doctor's advice. Do not use at all during the last 3 months of pregnancy.</p> <p>Ask your doctor or pharmacist before use of the medicine in children suffering from dehydration through diarrhoea and/or vomiting.</p> <p>Unless a doctor has told you to, do not use if you are aged 65 years or over.</p> <p>Unless a doctor has told you to, do not use in children 6 years of age or less.</p>
<p>Ibuprofen (Entry 4 of 6)</p>	<p>When included in a schedule to the SUSMP for oral use in children under 12 years of age</p>	<p>Do not use if you have a stomach ulcer.</p> <p>Do not use if you have impaired kidney function.</p> <p>Do not use if you have heart failure.</p> <p>Do not use if you are allergic to ibuprofen or other anti-inflammatory medicines.</p> <p>If you get an allergic reaction, stop taking and see your doctor immediately.</p> <p>Unless a doctor has told you to, do not use if you have asthma.</p> <p>Unless advised by your doctor or pharmacist, do not use with products containing ibuprofen, aspirin or other anti-inflammatory medicines or with medicines that you are taking regularly.</p> <p>Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful and</p>

		<p>increase the risk of heart attack, stroke or liver damage.</p> <p>Do not use if trying to become pregnant, or during the first 6 months of pregnancy, except on doctor's advice. Do not use at all during the last 3 months of pregnancy.</p> <p>Ask your doctor or pharmacist before use of the medicine in children suffering from dehydration through diarrhoea and/or vomiting.</p>
<p>Ibuprofen (Entry 5 of 6)</p>	<p>In combination with paracetamol, in medicines for oral use</p>	<p>Do not give to children under 12 years of age.</p> <p>Adults: Keep to the recommended dose. Do not take this medicine for longer than a few days at a time unless advised to by a doctor.</p> <p>Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.</p> <p>Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage.</p> <p>Do not use if pregnant or trying to become pregnant.</p> <p>Do not use if you have a stomach ulcer.</p> <p>Do not use if you have impaired kidney function.</p> <p>Do not use if you have heart failure.</p> <p>Do not use if you are allergic to ibuprofen or other anti-inflammatory medicines.</p> <p>If you get an allergic reaction, stop taking and see your doctor immediately.</p> <p>Unless a doctor has told you to, do not use if you have asthma.</p> <p>Unless a doctor has told you to, do not use if you are aged 65 years or over.</p> <p>Do not take with other products containing paracetamol, ibuprofen, aspirin or other anti-inflammatory medicines or with medicines that you are taking regularly, unless advised to do so by a doctor or pharmacist.</p> <p>If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26, New Zealand 0800 764 766) or go to hospital straight away even if you feel well because of the risk of delayed, serious liver damage.</p>
<p>Ibuprofen (Entry 6 of 6)</p>	<p>In preparations for dermal use</p>	<p>Do not use [this product/<i>insert name of product</i>] if you are allergic to ibuprofen or other anti-inflammatory medicines.</p> <p>If you get an allergic reaction, stop taking and see your doctor immediately.</p> <p>Unless a doctor or pharmacist has told you to, do not use [this product/<i>insert name of product</i>] with other medicines that you are taking regularly.</p>

### *International regulations*

XXXXX tablets (paracetamol 500 mg with ibuprofen 200 mg) have been approved as an over-the-counter medicine in many countries including the United Kingdom, Poland, New Zealand, Ukraine, Russia, Saudi Arabia, United Arab Emirates, Kuwait, Bahrain, Oman, Qatar and Yemen. It is Pharmacy Only in the United Kingdom and Poland and it is a 'general sale' medicine in New Zealand in pack sizes up to 20 dose units and 'pharmacy medicine' in pack sizes of up to 100 dose units. In the United Kingdom, XXXXX is available as a 'pharmacy' medicine in packs of up to 32 tablets.

XXXXXX tablets (paracetamol 500 mg with ibuprofen 150 mg) were approved in New Zealand in March 2009.

### *Summary of pre-meeting public submissions*

In response to [the notice published under regulation 42ZCZK](#) advising of the proposed amendment, five (5) submissions were received. All submissions opposed the amendment.

### **The main points provided in opposition to the proposed amendment were:**

- In June 2016, these products were down-scheduling to facilitate Schedule 2 supply, which coincided with an increase in calls to the Poisons Information Centres regarding overdoses involving these medicines.<sup>104</sup> The Medical Journal of Australia also recently published an article on paracetamol poisoning-related hospitalisations and deaths, demonstrating an increasing rate of paracetamol poisoning and associated harms between 2004 and 2017.<sup>105</sup>
- In 2018, the ACMS considered a proposal to amend the Schedule 3 entry for paracetamol, when combined with ibuprofen. The proposal sought to allow the Schedule 3 pack size to be increased from 30 dosage units (equivalent to 10 days' supply) to 50 dosage units (17 days' supply). The delegate's final decision published in November 2018 was to not amend the Poisons Standard on the basis that the perceived benefits of larger pack sizes from a convenience perspective were outweighed by the risks.<sup>106</sup>
- In 2018, the TGA published an interim decisions NOT to amend the Poisons Standard in relation to available pack sizes of paracetamol combined with ibuprofen.<sup>107</sup> We support the interim decision and considers there is no additional clinical evidence to support increasing pack sizes within the various Schedules nor to exempt the smallest pack size to allow general sale in supermarkets. The reduction in scheduling infers a perceived safety around use of these medicines.
- Although reduced maximum pack size of unscheduled paracetamol was implemented in Australia in 2013, there is no legal restriction on the number of packs that may be purchased in one transaction from non-pharmacy retail outlets, nor the means to generally monitor frequency of purchase.
- The risks associated with poisoning from these products due to therapeutic errors, inappropriate usage, accidental paediatric exposures and particularly deliberate self-poisonings, far outweighs the few benefits associated with changes to existing schedules. Since the introduction of combined paracetamol+ibuprofen products the number of calls received at NSW PIC regarding these products has substantially increased each year with 2019 currently showing a proportional increase in call numbers compared to 2018.
- The increasing number of calls regarding therapeutic errors also indicates ongoing confusion amongst the general public about the correct dosing of these products. Increasing the pack size available as an S2 medication and allowing pack sizes up to 12 to be unscheduled will further

<sup>104</sup> NPS Medicinewise (NSW June 2017). Dose confusion with paracetamol/ibuprofen combination s[cited 19 September 2019]; available at: <https://www.nps.org.au/news/dose-confusion-with-paracetamol-ibuprofen-combinations>

<sup>105</sup> Cairns R *et al.*, (2017). Paracetamol poisoning-related hospital admissions and deaths in Australia, 2004-2017. *Me J Aust* 211(5) 218-223; available at <https://www.mja.com.au/journal/2019/211/5/paracetamol-poisoning-related-hospital-admissions-and-deaths-australia-2004-2017>

<sup>106</sup> Therapeutic Goods Administration. Final decisions amending, or not amending, the current Poisons Standard, November 2018. 29 Nov 2018. At: <https://www.tga.gov.au/sites/default/files/final-decisions-amending-or-not-amending-current-poisons-standard-november-2018.pdf>

<sup>107</sup> ACSM #24. Publication of interim decisions proposing to amend, or not amend, the current Poisons Standard, September 2018: 1.6 Paracetamol combined with ibuprofen. [www.tga.gov.au/book-page/16-paracetamol-combined-ibuprofen](http://www.tga.gov.au/book-page/16-paracetamol-combined-ibuprofen) [accessed 17 September 2019]

increase the likelihood of incorrect dosage. The availability of larger pack sizes may also mean therapeutic errors will continue for longer before the patient discusses their medication use with a health professional such as a pharmacist or doctor.

- Existing marketed products containing paracetamol and ibuprofen combinations contain differing strengths and differing dose instructions that likely contribute to consumer confusion, highlighting the important need for accessibility to appropriate health professional review and counselling in the purchase of these products.
- The maximum recommended daily adult dose of paracetamol is 4 g. Single oral doses of paracetamol above 10 grams or 200 mg/kg of bodyweight, whichever is lower, have a reasonable likelihood of causing liver toxicity and irreversible damage. The proposed increases in pack size from 30 to 50 tablets would increase the total amount of paracetamol from 10 g to 25 g and ibuprofen from 6 g to 10 g.
- Ibuprofen should only be used with caution in consumers with coexisting medical conditions such as, asthma, heart conditions, gastrointestinal bleeding risk, or kidney disease and NSAIDs such as ibuprofen can interact with other medicines. Ongoing long-term treatment with any analgesic requires medical intervention especially when patients suffer additional conditions and already prescribed medicines that could interact with NSAIDs such as ibuprofen.
- The existing scheduling already provides adequate and appropriate consumer access to these combination products. It represents an adequate measure to address the risks by limiting the quantities that can be purchased without health professional advice. It is considered that the existing measures assist in protecting the public from unintended harms. As such, the proposed amendment to the scheduling of paracetamol/ibuprofen containing products is not supported.

#### *Summary of ACMS advice/recommendations to the Delegate*

The Committee recommended that the current scheduling of paracetamol (in combination with ibuprofen) in the Poison Standard remains appropriate.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (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 that the Secretary considers necessary to protect public health.

The reasons for the advice included:

52E(1) Considerations	Reasons
a – the risks and benefits of the use of a substance	<p><i>Risks:</i></p> <ul style="list-style-type: none"> <li>The risks associated with paracetamol-ibuprofen combinations are those of each ingredient with the additional risk of consumer confusion and therapeutic error.</li> <li>Pharmacist advice will not be available to mitigate risks of therapeutic error and inappropriate use if 12 dosage units are available for general sale (outside a pharmacy). As there are no limits on the number of unscheduled packs that may be purchased, the risk of intentional overdose is not mitigated. General sale also gives the impression of safety and paracetamol-ibuprofen combinations cannot be supplied with reasonable safety (SPF Handbook).</li> <li>Pharmacist advice is also likely to be significantly reduced if the Schedule 2 pack size is increased from 12 to 30 dosage units. Pharmacist intervention is required to manage acute pain, including inflammation and/or aches and pains associated with colds and flu. The current pack size of 12 dosage units is sufficient for initial use of combination analgesia, given that the</li> </ul>



	<p>combination is only to be used for a few days.</p> <ul style="list-style-type: none"> <li>• The risk of increasing the Schedule 2 pack size would be potentially delaying consumers seeking further advice from a health practitioner.</li> <li>• Potential increase in duration of inappropriate use and accidental poisoning due to a larger than necessary quantity being supplied under Schedule 3.</li> <li>• Risk of co-administration with other NSAIDs and analgesics</li> </ul>
b – the purposes for which a substance is to be used and the extent of use of a substance	<ul style="list-style-type: none"> <li>• Same as for the current Schedule 2 and Schedule 3 products. The substance is intended for use to provide temporary relief of acute pain and/or inflammation.</li> </ul>
c – the toxicity of a substance	<ul style="list-style-type: none"> <li>• The toxicity is well-established. Potential for significant toxicity if medication is taken over and above the recommended dosage from both ingredients.</li> <li>• Adverse effects in overdose of ibuprofen combined with paracetamol can be potentially severe. The adverse effects are liver damage, gastric ulcers, gastrointestinal bleeding, anaemia and melaena. Single oral doses of paracetamol above 10 grams or 200 mg/kg of bodyweight, whichever is lower, have a reasonable likelihood of causing liver toxicity and irreversible damage.</li> <li>• The proposed 30 dosage unit and 50 dosage unit pack size in Schedules 2 and 3 respectively increases the risk of harm from overdose.</li> </ul>
d – the dosage, formulation, labelling, packaging and presentation of a substance	<ul style="list-style-type: none"> <li>• The proposed warning statements for an unscheduled pack are the same as the Schedule 2 and 3 packs but without the availability of pharmacist advice.</li> </ul>
e – the potential for abuse of a substance	<ul style="list-style-type: none"> <li>• Increasing evidence of deliberate and accidental overdose according to PIC (NSW)</li> </ul>
f – any other matters that the Secretary considers necessary to protect public health	<ul style="list-style-type: none"> <li>• A previous application for paracetamol-ibuprofen combinations in 2018 was not approved based on the risks</li> <li>• There is a risk of consumer confusion in the market</li> <li>• Observed increasing trend in paracetamol overdoses</li> <li>• Pharmacist advice is required to deal with different types of pain and non-pharmacological management options.</li> </ul>

#### *Delegate's considerations*

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to paracetamol + ibuprofen;
- Advisory Committee on Medicines Scheduling's advice;
- The public submissions received by the [first closing date](#);
- Section 52E of the *Therapeutic Goods Act 1989*, 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 that the Secretary considers necessary to protect public health;
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and

- [Scheduling Handbook](#) (V 1.1, July 2019).

### *Reasons for the interim decision*

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and 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 that the Secretary considers necessary to protect public health.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the Scheduling Factors for Schedules 2, 3 and 4.

I have made an interim decision that the scheduling of paracetamol (in combination with ibuprofen) remains appropriate under Schedules 2, 3 and 4. I have set out my reasons below.

I have taken into account that the proposed increase in pack size is beyond the amount of medication required for acute pain and could encourage use of the medication for chronic pain. This does not meet the Scheduling Factors in the SPF (2018), especially for Schedule 2, which provides '*The use of the medicine is substantially safe for short term treatment and the potential for harm from inappropriate use is low*'.

I have considered that currently there are different strengths and dosages of the combination packs available and that this is likely to cause significant confusion in the community. In particular, the proposal for larger pack sizes may have the potential to increase the risk of over-dosage, both inadvertent and deliberate. There is also likely to be an assumption amongst consumers that if a product is available in a general retail outlet then it is safe for use and can be taken in combination with any other over-the-counter products. I am of the view that this may lead to inadvertent overdose if someone is not aware that they are taking paracetamol and/or ibuprofen in a combination product.

I have also taken into account that paracetamol combined with ibuprofen is not generally a first-line therapy for pain. These medications both have significant risk profiles particularly when taken in larger doses than the recommended daily dosages. In particular, ibuprofen has multiple contraindications and drug-drug interactions. As a result, ibuprofen should be used with caution by a large sector of the community (e.g. those over 65, those who suffer from asthma, heart conditions, renal disease, and gastrointestinal bleeding or are pregnant).

I have considered that the NSW Poisons Information Centre (PIC) data has shown a significant increase in calls regarding potential over-dosage of these medications since they were down-scheduled in 2015 to Schedule 2 for packs of 12 or less. Further, NSW PIC has taken an increasing number of calls each year regarding these combination medications in relation to therapeutic errors, deliberate self-poisoning and accidental poisoning, with the number of deliberate self-poisonings reported by 15 September 2019 already exceeding that of 2018 or any year previously, and total number of incidents since 2014.

I am of the view that the Applicant has not presented any further objective clinical evidence for the proposal to increase the pack sizes since the previous application in 2018 and I am in agreement with my [final decision](#) from November 2018. I am not in agreement with the proposal that states that the increase pack size in Schedules 2, 3 and 4, as well as the exemption of the smaller packs, is in the interest of public health and that the risk of misuse and inappropriate use is minimal. In particular, the Applicant has not acknowledged that each individual medication has the potential for serious harm, and when combined, may have more side effects than one of the medications alone.

I note that all five pre-meeting public submissions opposed the scheduling proposal on the grounds that the risks outweigh the benefits for increased pack sizes.

The current scheduling allows for the availability of clinically appropriate quantities for the treatment of acute/short-term pain while larger pack sizes are outside the acute pain relief indication and could encourage self-treatment for chronic pain. There is an increased risk of therapeutic error, misuse or overdose with larger pack sizes, which could lead to significant medical conditions. Overall the risks of these medications outweigh the purported benefits of the proposal.

## 1.6. Interim decision in relation to hyoscine butylbromide

### Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to hyoscine butylbromide as follows:

#### Schedule 4 – New Entry

**HYOSCINE BUTYLBROMIDE** **except** when included in Schedule 2 or 3.

#### Schedule 3 – New Entry

**HYOSCINE BUTYLBROMIDE** in undivided preparations for oral use with a recommended single dose not exceeding 20 mg of hyoscine butylbromide in a pack containing 100 mg or less of hyoscine butylbromide when labelled for adults and children 6 years and over.

#### Schedule 2

**HYOSCINE BUTYLBROMIDE** as the only therapeutically active substance, in divided preparations for oral use, containing 20 mg or less of hyoscine butylbromide per dosage unit in a pack containing 200 mg or less of hyoscine butylbromide.

#### Schedule 2 – Amend Entry

**HYOSCINE** ~~(excluding hyoscine butylbromide):~~

- a) for transdermal use in preparations containing 2 mg or less of total solanaceous alkaloids per dosage unit; or
- b) for oral use:
  - i) in undivided preparations containing 0.03 per cent or less of total solanaceous alkaloids, when labelled with a dose of 0.3 mg or less of total solanaceous alkaloids and a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids; or
  - ii) in divided preparations containing 0.3 mg or less of total solanaceous alkaloids per dosage unit when labelled with a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids.

#### Appendix H – New Entry

**HYOSCINE BUTYLBROMIDE**

#### Index – Amend Entry

**HYOSCINE BUTYLBROMIDE**

Schedule 4

Schedule 3

Schedule 2

Appendix H

#### *Proposed date of effect of the proposed amendment*

1 June 2020

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

##### *Applicant's scheduling proposal and reasons for the proposal*

An application to reschedule oral liquid dose form of hyoscine butylbromide from Schedule 4 to Schedule 2 in the Poisons Standard by removing the word 'divided' was considered.

The Applicant's proposed amendments to the Poisons Standard were:

### **Schedule 2 – Amend Entry**

HYOSCINE BUTYLBROMIDE as the only therapeutically active substance:

- a) in divided preparations for oral use, containing 20 mg or less of hyoscine butylbromide per dosage unit in a pack containing 200 mg or less of hyoscine butylbromide; **or**
- b) in undivided preparations for oral use with a recommended single dose not exceeding 20 mg of hyoscine butylbromide in a pack containing 100 mg or less of hyoscine butylbromide.

The Applicant's main points provided in support of the proposed amendment are as follows:

- The oral tablet dose form of this medicine containing either 10 mg or 20 mg of hyoscine butylbromide per tablet in preparations containing 200 mg or less is currently scheduled as a Schedule 2 (Pharmacy only) medicine in Australia. This application seeks to amend the Poisons Standard to classify the (undivided) oral liquid dose form for preparations containing 20 mg or less per dose unit in a pack containing 200 mg or less hyoscine butylbromide from a 'Prescription only' (Schedule 4) to a 'Pharmacy only' (Schedule 2) medicine. This will result in the harmonisation of the scheduling of the oral tablet and liquid dose forms when supplied in packs containing equivalent amounts of hyoscine butylbromide per dose unit and in the entire pack.
- Abdominal cramping and pain is not life-threatening, but it has a significant impact on the patient's quality of life and subsequent socioeconomic consequences (Lovell *et al.*, 2012).<sup>108</sup> Abdominal pain is one of most common reasons for people seeking medical care and hyoscine butylbromide has been proven to be safe and effective when used for relief from pain and discomfort of stomach cramps and spasm. The down-scheduling of the oral liquid dose will provide a significant benefit for paediatric and elderly patients, or other patient groups with dysphagia and difficulty swallowing the tablets (the currently available oral dose form, and classified under Schedule 2).
- The rescheduling of the oral liquid dose form of hyoscine butylbromide at the suggested strength in the respective pack size will not impose any safety risks to the Australian population as the total amount of active pharmaceutical ingredient being sold per pack is the same as in the oral tablet packs; and, control over the medicine is maintained as the pharmacist can refer the individual to their doctor to establish clinical need if they present symptoms that are potentially due to another underlying disorder or illness.

### *Current scheduling status*

Hyoscine butylbromide is currently listed in Schedule 2 of the Poisons Standard as follows:

### **Schedule 2**

HYOSCINE BUTYLBROMIDE as the only therapeutically active substance, in divided preparations for oral use, containing 20 mg or less of hyoscine butylbromide per dosage unit in a pack containing 200 mg or less of hyoscine butylbromide.

### **Index**

### **HYOSCINE BUTYLBROMIDE**

Schedule 2

The related substance hyoscine is currently listed in Schedule 4 and Schedule 2 and Appendix G of the Poisons Standard as follows:

### **Hyoscine**

### **Schedule 4**

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

<sup>108</sup> Lovell RM and Ford AC. (2012) Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis: Clinical gastroenterology and hepatology; 10: 712-721.

## Schedule 2

HYOSCINE (excluding hyoscine butylbromide):

- a) for transdermal use in preparations containing 2 mg or less of total solanaceous alkaloids per dosage unit; or
- b) for oral use:
  - i) in undivided preparations containing 0.03 per cent or less of total solanaceous alkaloids, when labelled with a dose of 0.3 mg or less of total solanaceous alkaloids and a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids; or
  - ii) in divided preparations containing 0.3 mg or less of total solanaceous alkaloids per dosage unit when labelled with a recommended daily dose of 1.2 mg or less of total solanaceous alkaloids.

## Appendix G

Column 1	Column 2
Poison	Concentration (quantity per litre or kilogram)
HYOSCINE	300 micrograms

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### HYOSCINE

cross reference: HYOSCINE BUTYLBROMIDE

Schedule 4

Schedule 2

Appendix G

### *Scheduling history*

#### Hyoscine

In May 1956, hyoscine (and its derivatives) was included in the Poisons Standard in Schedule 1 (then requiring a license to dispense and purchase – Schedule 1 is now no longer in use) in preparations more than 0.25% and in Schedule 2 at less than 0.25%. In the February 1975, as part of a scheduling overhaul, the Schedule 1 entry for hyoscine was moved to Schedule 3. In November 1985, transdermal applicators of 2 mg or less of hyoscine were permitted in Schedule 2 for motion sickness.

In August 1992, a new Appendix G (dilute preparations) in Part 5 of the Poisons Standard was created and hyoscine was included in this amendment at 10 micrograms.

#### Hyoscine butylbromide

Hyoscine butylbromide was first included in Schedule 4 of the Poisons Standard in February 1967.

In November 1969, hyoscine butylbromide was exempt from the scheduling entries of hyoscine (and hyoscyamine) as part of editorial amendments for scheduling irregularities.

In November 1988, the Schedule 4 entry for hyoscine butylbromide was deleted and a new Schedule entry for hyoscine was included, which captured hyoscine butylbromide. No reason for this decision was minuted.

In November 1993, the Drugs and Poisons Schedule Standing Committee (DPSSC) rejected an application to reschedule hyoscine butylbromide from Schedule 4 to Schedule 3 on the basis that it had received advice from a professional body that there was no place for hyoscine butylbromide in the treatment of irritable bowel syndrome.

In April 1994, the DPSSC considered information relating to the rescheduling of hyoscine butylbromide from Schedule 4 to Schedule 3 and agreed to finalise an ongoing review of solanaceous alkaloids (including hyoscine butylbromide) and to also conduct a review of the scheduling of them.

In August 1994, the National Drug and Poisons Schedule Committee (NDPSC) considered a large amount of information relating to the safety and efficacy of hyoscine butylbromide and were satisfied with its safety profile. However, the Committee considered that a comprehensive review still needed to be undertaken and requested that all relevant information be obtained from other sponsors of hyoscine butylbromide. This information was reviewed at the November 1994 NDPSC meeting, and it was agreed that hyoscine butylbromide should be included in Schedule 3 with dose and pack size restrictions.

In May 1998, the NDPSC considered a submission to reschedule hyoscine butylbromide to Schedule 2. However, due to concerns about mandatory pharmacist advice being required, the Committee decided that the Schedule 3 classification remained appropriate. The August 1998 NDPSC meeting reconsidered this decision with new evidence presented and felt that this new evidence addressed its concerns regarding access and use without pharmacist advice. The Committee agreed to include hyoscine butylbromide in Schedule 2.

In [November 2001](#), in considering the scheduling of solanaceous plants and alkaloids, the NDPSC decided on a number of principles to be adopted for inclusion of preparations containing solanaceous plants and alkaloids in Schedule 2. As a consequence, the Schedule 2 entry for hyoscine was amended to specifically exclude hyoscine butylbromide.

In [June 2002](#), the NDPSC considered an application to amend the wording of the Schedule 2 entry for hyoscine butylbromide to increase the dosage per unit from 10 mg to 20 mg or less of hyoscine butylbromide and to amend the pack size from 20 or less dosage units to 200 mg or less of hyoscine butylbromide. The Committee agreed to amend the Schedule 2 entry on the basis of a long history of safe use and there being no significant safety concerns with hyoscine butylbromide at the current Schedule 2 dose and pack size.

In [February 2005](#), the NDPSC considered the harmonisation of the scheduling of hyoscine butylbromide with New Zealand. The New Zealand Medicines Classification Committee (MCC) expressed reservations with regards the down scheduling of hyoscine butylbromide to Schedule 2, with the need for consultation over abdominal pain. MCC members agreed that misdiagnosis was easy and there was a danger, even with a 4-day pack, that the product could be used for acute appendicitis, renal stones or gastric ulcers and that bowel problems could be masked. There were also concerns associated with cardiac arrhythmia and glaucoma and with interactions with other medicines. The Trans-Tasman Harmonisation Working Party's advice to the NDPSC was that, having regard to the established safety in use of products containing hyoscine butylbromide over an extensive period and in the interests of harmonisation, the New Zealand Ministry of Health reconsider harmonisation of scheduling with the Poisons Standard. The Committee accepted the Working Party's advice and agreed to recommend to the New Zealand Ministry of Health that the scheduling of hyoscine butylbromide be harmonised with Australia.

In [October 2007](#), the NDPSC considered a proposal to amend the Schedule 2 entry of hyoscine butylbromide to increase the pack size restriction from 200 mg to 500 mg and remove the single active substance restriction from the Schedule 2 entry. The Committee rejected the proposal after consideration of public consultation and an expert evaluation report and that RASML should be contacted to include a warning label on all anticholinergic products including hyoscine butylbromide.

#### *Australian regulations*

- According to the [TGA Database](#), hyoscine butylbromide is:
  - Available for use as an active ingredient in: Biologicals, Export Only, Over the Counter and Prescription Medicines;
  - Available for use as an excipient ingredient in: Biologicals, devices, Prescription Medicines; and
  - Not available as an equivalent ingredient in any application.



- There are eighteen (18) medicines as of 31 May 2018 active on the [Australian Register of Therapeutic Goods \(ARTG\)](#) containing hyoscine butylbromide as an active ingredient. These include six (6) prescription and twelve (12) non-prescription medicines.
- Hyoscine butylbromide is not permitted to be included in listed medicines as it is not included in the current [Therapeutic Goods \(Permissible Ingredients\) Determination No.4 of 2019 \(the Determination\)](#)<sup>109</sup>. However, hyoscine and hyoscyamine are in the Determination as follows:

Item	Ingredient name	Purpose	Specific requirements
2634	HYOSCYAMUS LEAF DRY	A, H	<p>Alkaloids calculated as hyoscyamine and hyoscine are mandatory components of Hyoscamus leaf dry.</p> <p>The concentration of alkaloids calculated as hyoscyamine in the medicine must be no more than 300 micrograms/Kg or 300 micrograms/L or 0.00003%.</p> <p>The concentration of hyoscine in the medicine must be no more than 300 micrograms/kg or 300 micrograms/L or 0.00003%.</p>
2635	HYOSCYAMUS LEAF POWDER	A, H	<p>Alkaloids calculated as hyoscyamine and hyoscine are mandatory components of Hyoscamus leaf powder.</p> <p>The concentration of alkaloids calculated as hyoscyamine in the medicine must be no more than 300 micrograms/Kg or 300 micrograms/L or 0.00003%.</p> <p>The concentration of hyoscine in the medicine must be no more than 300 micrograms/kg or 300 micrograms/L or 0.00003%.</p>
2636	HYOSCYAMUS NIGER	A, H	<p>Alkaloids calculated as hyoscyamine and hyoscine are mandatory components of Hyoscyamus niger.</p> <p>The concentration of hyoscyamine in the medicine must be no more than 3 micrograms/kg or 3 micrograms/L or 0.3%.</p> <p>The concentration of hyoscine in the medicine must be no more than 300 micrograms/kg or 300 micrograms/L or 0.00003%.</p>

A = active ingredient for a medicine has the same meaning as in the Regulations  
H = homoeopathic preparation ingredient meaning an ingredient that is a constituent of a homoeopathic preparation

<sup>109</sup> <https://www.legislation.gov.au/Details/F2019L01597>



- The [Prescribing medicines in pregnancy database](#)<sup>110</sup> classifies hyoscine-*N*-butylbromide as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Hyoscine- <i>N</i> -butylbromide	B2	Alimentary System	Antispasmodics	-
Hyoscine- <i>N</i> -butylbromide	B2	Cholinergic and Anticholinergic Agents	-	-
<p><b>Category B2</b> – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.</p>				

- The Medicines Advisory Statement Specification 2019 ([RASML No. 5 – Schedule 1](#))<sup>111</sup> does not specifically list hyoscine butylbromide. However, hyoscine, hyoscyamine and *Hyoscyamus niger* require the following warning statements to be included on the labelling:

Column 1 Substance(s)	Column 2 Conditions	Column 3 Required statements(s)
Hyoscine	In preparations for oral use, EXCEPT where indicated exclusively for the treatment of motion/travel sickness	<ul style="list-style-type: none"> <li>If the condition persists after two days of treatment, seek medical advice as soon as possible.</li> </ul>
Hyoscyamine	In preparations for oral use, EXCEPT where indicated exclusively for the treatment of motion/travel sickness	<ul style="list-style-type: none"> <li>If the condition persists after two days of treatment, seek medical advice as soon as possible.</li> <li>Do not use during pregnancy or breastfeeding unless advised by your doctor or pharmacist</li> </ul>
<i>Hyoscyamus niger</i>	In preparations for oral use, EXCEPT where indicated exclusively for the treatment of motion/travel sickness	<ul style="list-style-type: none"> <li>If the condition persists after two days of treatment, seek medical advice as soon as possible.</li> </ul>

- The [Database of Adverse Event Notifications \(DAEN\)](#)<sup>112</sup> contains 205 reports of adverse events for products containing hyoscine butylbromide as an active ingredient, with 102 reports where hyoscine butylbromide was the single suspected medicine. There was one (1) report of death associated with hyoscine butylbromide use.
- As of 31 May 2019, there is one (1) hyoscine butylbromide active constituent approval (XXXXX) and one product (XXXXX) containing hyoscine butylbromide listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#).

<sup>110</sup> <https://www.tga.gov.au/prescribing-medicines-pregnancy-database>

<sup>111</sup> <https://www.legislation.gov.au/Details/F2019L00213>

<sup>112</sup> <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

### International regulations

Hyoscine butylbromide preparations are currently available in 41 countries worldwide.<sup>113</sup> Hyoscine butylbromide was first registered in Germany in 1951 and became commercially available in 1952. Since then, it has become a widely available medication worldwide, both as a prescription drug and an OTC medicine in several countries.<sup>114</sup> Hyoscine butylbromide is currently registered as an OTC product in Belgium, Germany, Italy, Luxembourg, the Netherlands, Spain, Switzerland, the United Kingdom (UK), Argentina, Colombia, Mexico, Venezuela, Japan and South Korea.<sup>115</sup>

- Hyoscine butylbromide is on the [World Health Organisation's Model List of Essential Medicines](#)<sup>116</sup> in *Section 2.3 Medicines for other common symptoms in palliative care* (Injection: 20 mg/mL).
- The European Chemicals Agency (ECHA)<sup>117</sup> hazard classification and labelling for hyoscine butylbromide is as follows: *'Danger.....this substance is harmful if swallowed, is harmful if inhaled and causes serious eye damage.'*
- Hyoscine butylbromide is not available in the United States.
- Injectable hyoscine butylbromide is included on Health Canada's [Prescription Drug List](#) for both human and veterinary use with the qualifier, *'when recommended for parenteral use'*. Hyoscine butylbromide non-injectable is also available as an 'ethical' medicine for human use,<sup>118</sup> i.e. a drug that does not require a prescription, but is generally prescribed by a medical practitioner.<sup>119</sup>
- In the UK, hyoscine butylbromide, as XXXXXXXXXXXXX, is included in the ['General sales List \(GSL\)'](#) and is available off the shelf in a variety of shops including newsagents, convenience stores, petrol stations etc.(i.e. no pharmacy training is required to sell). Hyoscine butylbromide, as XXXXXXXXXXXXX only available as a Pharmacist medicine.<sup>120</sup>

### Summary of pre-meeting public submissions

In response to [the notice published under regulation 42ZCZK](#) advising of the proposed amendment, three (3) submissions were received. One (1) submission supported the amendment and two (2) submissions opposed the amendment.

#### The main points provided in support of the proposed amendment were:

- This amendment provides for a set amount of liquid (in undivided oral doses) hyoscine butylbromide per pack to be available within Schedule 2. This aligns with the current scheduling of oral tablet formulation and enhances access without a prescription to a liquid formulation for treatment of abdominal cramping and pain.

#### The main points provided in opposition to the proposed amendment were:

- In New Zealand, hyoscine butylbromide in the forms and amounts equivalent to Schedule 2 in Australia are classified as Restricted. While there were not major concerns about the inherent safety of the substance, the scheduling of hyoscine butylbromide across the two countries was not harmonised in 2005 as the New Zealand regulator was concerned about "the very broad indication for abdominal pain" and felt "there should be an opportunity to refer consumers to a medical practitioner if they were suffering from abdominal pain".<sup>121</sup>

<sup>113</sup> Martindale [online via MedicinesComplete]: <https://about.medicinescomplete.com/publication/martindale-the-complete-drug-reference/>

<sup>114</sup> Tytgat, G.N. (2007) Hyoscine Butylbromide. A Review of its Use in the Treatment of Abdominal Cramping and Pain. *Drugs*, 67(9): 1343 – 1357.

<sup>115</sup> Tytgat, G.N. (2007) Hyoscine Butylbromide. A Review of its Use in the Treatment of Abdominal Cramping and Pain. *Drugs*, 67(9): 1343 – 1357.

<sup>116</sup> <https://www.who.int/medicines/publications/essentialmedicines/en/>

<sup>117</sup> <https://echa.europa.eu/substance-information/-/substanceinfo/100.005.223>

<sup>118</sup> <https://health-products.canada.ca/dpd-bdpp/dispatch-repartition.do>

<sup>119</sup> <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database/terminology.html>

<sup>120</sup> <https://www.nhs.uk/medicines/buscopan-hyoscine-butylbromide/>

<sup>121</sup> New Zealand Medicines and Medical Devices Safety Authority (Medsafe). Minutes of the 33rd meeting of the Medicines Classification Committee. 9 Jun 2005. At: <https://www.medsafe.govt.nz/profs/class/Minutes/2001-2005/mccMin9June2005.htm>

- Due to its physicochemical characteristics, hyoscine butylbromide cannot readily cross the blood-brain barrier and is therefore associated with a lower frequency of central nervous system side effects. Nevertheless, there are reported cases<sup>122, 123</sup> of intentional misuse of hyoscine butylbromide (in tablet form) through crushing and smoking for its hallucinogenic effects. The Product Information for a registered product of hyoscine butylbromide also states that it may cause drowsiness.<sup>124</sup> The liquid form may be considered a more convenient option by those who intentionally misuse the product.
- The TGA-approved indications for the currently marketed products that contain hyoscine butylbromide include for the treatment of spasm of the gastrointestinal tract. In severe cases, unexplained abdominal pain can persist or worsen or can occur together with symptoms like fever, nausea, vomiting, changes in bowel movements, abdominal tenderness, decreased blood pressure, fainting or blood in stool. In these cases, medical advice should immediately be sought.
- The currently marketed product containing the substance states that the tablets are not recommend for children under 6 years of age. Given that consumers will assume that a liquid presentation is especially formulated for children, the public submission notes that they do not believe that it would be appropriate for this product to be Schedule 2.
- While there is probably little potential for abuse of this substance, there may be a potential for inadvertent misuse as was seen with the infant colic drops, which were the subject of the Australian Prescriber article 'Dosing errors with XXXXXXXXXXXXXXXX'.<sup>125</sup> Given there is currently no product registered on the ARTG there is no compelling reason to down-schedule hyoscine butylbromide from Schedule 4. Therefore, the current scheduling remains appropriate.
- Oral liquid dose form of hyoscine butylbromide may be of benefit for paediatric and elderly patients, or other patient groups with dysphagia and difficulty swallowing the tablet formulation. However, these are regarded as more vulnerable population groups where the risk of adverse effects is higher and professional intervention would be beneficial to ensure patient safety and quality use of medicines.
- A preference for pharmacist oversight in the handling and provision of liquid preparations of hyoscine butylbromide is indicated. Therefore, inclusion of liquid oral preparations of hyoscine butylbromide with a recommended single dose not exceeding 20 mg of hyoscine butylbromide in a pack containing 100 mg or less of hyoscine butylbromide should be included in Schedule 3 rather than Schedule 2.

#### *Summary of ACMS advice/recommendations to the Delegate*

The Committee recommended that a new Schedule 3 entry for undivided preparations of hyoscine butylbromide be created in the Poisons Standard as follows:

#### **Schedule 3 – New Entry**

**HYOSCINE BUTYLBROMIDE in undivided preparations for oral use with a recommended single dose not exceeding 20 mg of hyoscine butylbromide in a pack containing 100 mg or less of hyoscine butylbromide when labelled for adults and children 6 years and over.**

The Committee also recommended an implementation date of 1 June 2020.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (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 that the Secretary considers necessary to protect public health.

<sup>122</sup> Public Health England. Misuse of hyoscine butylbromide (XXXXXXX) [letter]. 25 Jun 2015. At: <https://medicines.necsu.nhs.uk/wp-content/uploads/2015/07/MisuseXofXhyoscineXbutylbromideXletterXV5XFinal.pdf>

<sup>123</sup> Jalali F, Afshari R, Babaei A. Smoking crushed hyoscine/scopolamine tablets as drug abuse. *Subst Use Misuse* 2014;49(7):797–7.

<sup>124</sup> Australian Product Information – XXXXXXX and XXXXXXX (hyoscine butylbromide). 19 Sep 2018.

<sup>125</sup> <https://www.nps.org.au/australian-prescriber/articles/dosing-errors-with-donnalix-infant-drops>

The reasons for the advice included:

52E(1) Considerations	Reasons
a – the risks and benefits of the use of a substance	<ul style="list-style-type: none"> <li>Hyoscine butylbromide has a favourable benefit-risk profile and has proven to be safe and effective in treatment. It has low absorption and bioavailability after oral administration and therefore minimal side effects. It also has short elimination half-life therefore any side effects are mild and short lived. Making the agent available in a liquid form as a Schedule 3 medicine is unlikely to impact the risk-benefit profile significantly.</li> <li>To maximise safe use of hyoscine butylbromide, access to advice from a pharmacist should be available as per Schedule 3 medicines.</li> <li>There is a risk of hyoscine butylbromide masking more serious medical conditions. This risk can be minimised through pharmacist-consumer consultation.</li> </ul>
b – the purposes for which a substance is to be used and the extent of use of a substance	<ul style="list-style-type: none"> <li>Hyoscine butylbromide is used for the treatment of abdominal pain and discomfort in adults and children, irritable bowel syndrome and dysmenorrhoea.</li> </ul>
c – the toxicity of a substance	<ul style="list-style-type: none"> <li>Hyoscine butylbromide is well tolerated following oral administration due to its low oral bioavailability with no clinically significant differences between tablets and liquid.</li> <li>There is a low frequency of adverse events.</li> </ul>
d – the dosage, formulation, labelling, packaging and presentation of a substance	<ul style="list-style-type: none"> <li>There is a potential that consumers may assume that a liquid preparation of hyoscine butylbromide is intended for young children. There is no evidence for hyoscine butylbromide use in those less than 6 years.</li> </ul>
e – the potential for abuse of a substance	<ul style="list-style-type: none"> <li>There are minimal isolated reports of abuse of hyoscine butylbromide in prison populations.</li> </ul>
f – any other matters that the Secretary considers necessary to protect public health	<ul style="list-style-type: none"> <li>Functional gastrointestinal disorders are common in children. Australian clinicians have reported that there is parental pressure to find an immediate cure (Journal of Paediatrics and Child Health 55 (2019) 1063–1069), which in turn increases the risk of potential likelihood of inappropriate use of a liquid preparation of hyoscine butylbromide in children.</li> </ul>

#### *Delegate's considerations*

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to hyoscine butylbromide;
- Advisory Committee on Medicines Scheduling's advice;
- The public submissions received by the [first closing date](#);

- Section 52E of the *Therapeutic Goods Act 1989*, 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 that the Secretary considers necessary to protect public health;
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- [Scheduling Handbook](#) (V 1.1, July 2019).

#### *Reasons for the interim decision*

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (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 that the Secretary considers necessary to protect public health.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the Scheduling Factors for Schedule 2 and 3.

I have made an interim decision to amend the Poisons Standard by creating new Schedule 3 and 4 entries for hyoscine butylbromide and I have set out my reasons below.

I have taken into consideration that there are currently no Australian Register of Therapeutic Goods (ARTG) listed liquid preparations for oral use of hyoscine butylbromide. However, there are liquid ampoules containing 20 mg/mL hyoscine butylbromide for intravenous and intramuscular injections (Schedule 4 prescription medicines) on the ARTG.

I note that hyoscine butylbromide has been commercially available since 1952 and it is a well-tolerated medicine with a long history of worldwide over the counter experience. Side effects are uncommon, as hyoscine butylbromide has low absorption and bioavailability, does not cross the blood brain barrier and is not associated with central nervous system adverse effects as seen with other hyoscine compounds. Further, there are no clinically significant differences between hyoscine butylbromide tablets and liquid. However, on balance, I am of the opinion that undivided preparations of hyoscine butylbromide do not meet the Scheduling Factors for inclusion in Schedule 2 as there is no evidence for the use of hyoscine butylbromide in those aged less than 6 years. If hyoscine butylbromide were to be a Schedule 2 medicine available as a liquid form for oral use, I am concerned that consumers may assume that a liquid preparation is intended for use in young children to treat conditions such as functional gastrointestinal disorders (FGIDs), which are common in children.

I consider that undivided preparations of hyoscine butylbromide better meet the Scheduling Factors for Schedule 3, as it has a favourable risk-benefit profile. The availability of access to advice from a pharmacist via a Schedule 3 listing will ensure its safe and quality use. Further, the down-scheduling of the oral liquid to Schedule 3 will provide a significant benefit to more vulnerable patient groups with dysphagia and difficulty swallowing the tablet form.

I have also made a decision to create a new Schedule 4 entry for hyoscine butylbromide and to remove the reference to hyoscine butylbromide in the Schedule 2 entry for hyoscine. I am of the view that as hyoscine butylbromide is specifically scheduled in Schedule 2, then it is potentially not captured outside of this by the Schedule 4 entry for hyoscine. By creating a specific Schedule 4 entry for hyoscine butylbromide in addition to the Schedule 2 and 3 entries, this will help provide clarity and remove ambiguity of the scheduling of hyoscine butylbromide outside the schedule entries of hyoscine.

As part of the review of the [Scheduling Policy Framework](#) (SPF), it was decided that advertising of medicines containing Schedule 3 substances should be permitted unless there was reason not to. In order for these medicines to be lawfully advertised, they need to be included in Appendix H of the Poisons Standard. Having considered the matters set out in the [Guidelines for advertisements for medicines containing Schedule 3 substances](#) I am satisfied that there are no foreseeable potential impacts on public health that would preclude advertising hyoscine butylbromide directly to consumers and have decided that it should be included in Appendix H.

## 1.7. Interim decision in relation to Lidocaine

### Interim decision

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

#### Schedule 2 – Amend Entry

LIDOCAINE in preparations for topical use other than eye drops:

- a) containing 10 per cent or less of total local anaesthetic substances, **except:**
  - i) in dermal preparations containing 2 per cent or less of total local anaesthetic substances; or
  - ii) in aqueous sprays for oromucosal use containing 0.6 per cent or less of total local anaesthetic substances; or
- b) in divided preparations containing 200 mg or less of total local anaesthetic substances, **except** in lozenges containing 30 mg or less of total local anaesthetic substances per dosage unit.

#### *Proposed date of effect of the proposed amendment*

1 June 2020

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

##### *Applicant's scheduling proposal and reasons for the proposal*

An application to amend the Schedule 2 entry for lidocaine in the Poisons Standard was considered.

The Applicant's proposed amendments to the Poisons Standard were:

#### Schedule 2 – Amend Entry

LIDOCAINE in preparations for topical use other than eye drops:

- a) containing 10 per cent or less of total local anaesthetic substances, **except:**
  - i) in dermal preparations containing 2 per cent or less of total local anaesthetic substances; **or**
  - ii) in aqueous sprays for oromucosal use containing 0.6 per cent or less of total local anaesthetic substances; or
- b) in divided preparations containing 200 mg or less of total local anaesthetic substances, **except** in lozenges containing 30 mg or less of total local anaesthetic substances per dosage unit.

The Applicant's main points provided in support of the proposed amendments were as follows:

- Lidocaine 0.6% throat sprays can appropriately be classified as 'exempted from scheduling' as set out in the Scheduling Handbook.
- Lidocaine 0.6% throat sprays can be supplied with reasonable safety and without any access to health professional advice on the same basis that lidocaine throat lozenges are currently available at higher doses without access to health professional advice.
- The proposed amendment meets and exceeds all of the factors for Schedule 2.
- There are legitimate reasons for people to prefer the use of a low-dose spray in preference to a lozenge in relieving the pain of a sore throat.



- Changing the classification of lidocaine 0.6% throat sprays to unscheduled will allow people to choose between those dose forms without having to visit a pharmacy.

### *Scheduling history*

Lidocaine is currently listed in Schedules 2, 4 and 5 of the Poisons Standard as follows:

#### **Schedule 5**

LIDOCAINE in aqueous gel preparations containing 4.5 per cent or less of lidocaine, for the dermal spray-on administration to post-surgical wounds associated with 'mulesing' of sheep; tail docking and castration of lambs; or castration and disbudding/dehorning in calves.

#### **Schedule 4**

LIDOCAINE **except**:

- a) when included in Schedules 2 or 5;
- b) in dermal preparations containing 2 per cent or less of total local anaesthetic substances per dosage unit; or
- c) in lozenges containing 30 mg or less of total anaesthetic substances per dosage unit.

#### **Schedule 2**

LIDOCAINE in preparations for topical use other than eye drops:

- a) containing 10 per cent or less of total local anaesthetic substances, except in dermal preparations containing 2 per cent or less of total local anaesthetic substances; or
- b) in divided preparations containing 200 mg or less of total local anaesthetic substances, except in lozenges containing 30 mg or less of total local anaesthetic substances per dosage unit.

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#### **LIDOCAINE**

Schedule 5

Schedule 4

Schedule 2

There are other local anaesthetics listed in the Poisons Standard as follows:

#### **Schedule 5**

BUPIVACAINE in aqueous gel preparations containing 0.5 per cent or less of bupivacaine, for the dermal spray-on administration to post-surgical wounds associated with 'mulesing' of sheep; tail docking and castration of lambs; or castration and disbudding/dehorning in calves.

#### **Schedule 4**

ARTICAINE.

BUPIVACAINE **except** when included in Schedule 5.

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

ETIDOCAINE.

LEVObUPIVACAINE.

MEPIVACAINE.

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



PROCAINE.

ROPIVACAINE.

TETRACAINE **except**:

- a) when included in Schedule 2; or
- b) in dermal preparations containing 2 per cent or less of total local anaesthetic substances.

## Schedule 2

BENZOCAINE in preparations for topical use other than eye drops:

- a) containing 10 per cent or less of total local anaesthetic substances, **except** in dermal preparations containing 2 per cent or less of total local anaesthetic substances; or
- b) in divided preparations containing 200 mg or less of total local anaesthetic substances per dosage unit, except in lozenges containing 30 mg or less of total local anaesthetic substances per dosage unit.

CINCHOCAINE in preparations for topical use other than eye drops, containing 0.5 per cent or less of total local anaesthetic substances.

PRILOCAINE in preparations for dermal use containing 10 per cent or less of total local anaesthetic substances.

TETRACAINE in preparations for topical use other than eye drops, containing 10 per cent or less of total local anaesthetic substances **except** in dermal preparations containing 2 per cent or less of total local anaesthetic substances.

### *Scheduling history*

The TGA is currently [harmonising medicine ingredient names](#) and are updating some medicine ingredient names used in Australia to align with names used internationally. Lidocaine was previously scheduled under the name lignocaine. As a result, the two names are used interchangeably in the scheduling history.

In November 1987, the Drugs and Poisons Schedule Committee (DPSC) recommended that a new Schedule 4 entry for lignocaine be created given that the proposed use of a cream product (2.5% lignocaine and 2.5% prilocaine) requires medical supervision and approval. The Committee also noted that the similar substance, prilocaine was already listed in Schedule 4. There is no information available on when lignocaine was first entered into Schedule 2 of the Poisons Standard.

In August 1994, the National Drugs and Poisons Schedule Committee (NDPSC) considered a request to review the clarity of the definition of '*topical use*' and '*internal use*' as they apply to local anaesthetic substances. Lignocaine preparations could be classified as both for topical use, as they produce a localised effect, and as internal use, as most can only be administered orally. The Applicant raised concern that while these products should be classified as Schedule 2 ('LIGNOCAINE preparations for topical use, other than eye drops, containing 10% or less of local anaesthetic substance'), they may also be considered as Schedule 4 (entry wording not found in historical documents) as lignocaine products are used on areas of the body to which the definition topical and internal use apply. The Committee noted that the definition for internal use does not preclude topical use. It is this anomaly that the Committee agreed required further consideration pending advice from the states and territories.

In February 1998, the NDPSC considered a submission for the rescheduling of dermal preparations containing one (1) per cent or less of lignocaine in packs of 30 g or less from Schedule 2 to unscheduled. Noting that 14 out of 15 products containing ≤1% of lignocaine present on the Australian Register of Therapeutic Goods (ARTG) had 'grandfathered' status, for which indications for use were not included on the ARTG and considering the adverse reaction profile of lignocaine, the Committee decided that based on the use pattern at that time, lignocaine should remain a scheduled substance. This decision was affirmed in May 1998 following the Committee's reconsideration of the Applicant's comments, and subsequent examination of public comments.

In February 2001, the NDPSC decided to amend the Schedule 2 and Schedule 4 entries for lignocaine so that the entries were expressed in terms of total local anaesthetic substances. The Committee also considered and agreed to a recommendation from the Trans-Tasman Harmonisation Working Party that two (2) per cent lignocaine or less in dermal preparations should be exempted from scheduling.

In February 2002, the NDPSC reviewed all the local anaesthetic substance entries in the Poisons Standard to ensure that all cut-offs are defined in terms of the total local anaesthetic substance content for consistency. The rationale was to ensure that the cut-offs were consistent and defined in terms of the 'total local anaesthetic substance' content. Following examination of entries for local anaesthetic substances, the Committee noted that the entries appeared to have the appropriate cut-off definition and that no further action was required.

In October 2008, the NDPSC considered a proposal to broaden the Schedule 2 exemption for lidocaine for dermal use (at 2% or less) to also include use on gums. The application was based around a teething gel containing 2% choline salicylate combined with 0.5% lignocaine. The Committee decided to retain the current Schedule 2 entry based on concerns around the potential for over-use and possible adverse effects in infants and young children.

### *Australian regulations*

Lidocaine is an approved active ingredient in both veterinary and human medicines, with a long history of use.

- According to the [TGA Ingredient Database](#),<sup>126</sup> lidocaine (lignocaine) and is:
  - Available for use as an Active Ingredient in: Biologicals, Export Only, Over the Counter, Prescription Medicines;
  - Available for use as an Excipient Ingredient in: Biologicals, Devices, Prescription Medicines; and
  - Available for use as an Equivalent Ingredient in: Prescription Medicines.
- There are 188 products containing lidocaine, lidocaine hydrochloride and lidocaine hydrochloride monohydrate for therapeutic use currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#).<sup>127</sup> Of these 188 products, 38 are prescription medicines and 94 are non-prescription medicines. The formulation types include spray (aerosol), ointment, gel, lozenges, dermal patches, medicated dressings, cream, pellets, lotion, liquid, jelly and injectables.
- There are 18 lozenge/throat spray products listed on the [Australian Register of Therapeutic Goods](#)<sup>128</sup> (ARTG) as of January 2019. These products contain up to 30 mg lidocaine per lozenge and all of these products are unscheduled. XXXXXXXXXXXXXXXXXXXX at 0.78 mg lidocaine per spray remains the only spray product on the ARTG and this product is currently in Schedule 2.
- Lidocaine is not permitted to be used in listed medicines as it is not included in the current [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2019](#).<sup>129</sup>
- The [Prescribing medicines in pregnancy database](#)<sup>130</sup> classifies lidocaine as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Lidocaine	A	Cardiovascular System	Antiarrhythmics	-
Lidocaine	A	Drugs Used in Anaesthesia	Local anaesthetics	-

<sup>126</sup> <https://www.ebs.tga.gov.au/>

<sup>127</sup> <https://www.tga.gov.au/artg>

<sup>128</sup> <https://www.tga.gov.au/artg>

<sup>129</sup> <https://www.legislation.gov.au/Details/F2019L01597>

<sup>130</sup> <https://www.tga.gov.au/prescribing-medicines-pregnancy-database>

Lignocaine (lidocaine)	A	Cardiovascular System	Antiarrhythmics	-
Lignocaine (lidocaine)	A	Drugs Used in Anaesthesia	Local anaesthetics	-
<b>Category A</b> – Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.				

- The [Medicines Advisory Statement Specification 2019 \(RASML No. 5 – Schedule 1\)](#)<sup>131</sup> requires the following warning statements pertaining to lidocaine to be included on the labelling:

Substance	Conditions	Required statements
Lidocaine (Lignocaine) (Entry 1 of 3)	In dermal preparations containing MORE THAN 2 per cent of total local anaesthetic substances	<ul style="list-style-type: none"> <li>Do not apply to large areas of the body, except on the advice of a healthcare practitioner.</li> <li>If skin irritation occurs, discontinue use and seek advice from your doctor or pharmacist.</li> </ul>
Lidocaine (Lignocaine) (Entry 2 of 3)	In dermal preparations containing 2 per cent OR LESS of total local anaesthetic substances	<ul style="list-style-type: none"> <li>If skin irritation occurs, discontinue use and seek advice from your doctor or pharmacist.</li> </ul>
Lidocaine (Lignocaine) (Entry 3 of 3)	In lozenges	<ul style="list-style-type: none"> <li>Do not take hot food or drink if the mouth feels numb after taking this product as it may burn the mouth.</li> <li>Do not give to children under 6 years of age, unless recommended by a doctor, pharmacist or dentist.</li> </ul>

- The [Database of Adverse Event Notifications \(DAEN\)](#)<sup>132</sup> contains 906 reports of adverse events for products containing lidocaine as an active ingredient, with 511 reports where lidocaine was the single suspected medicine. There were 16 reports of deaths associated with lidocaine use.
- There are seventy five (75) products containing lidocaine listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#).<sup>133</sup> Twenty-three products contain lidocaine as an active constituent.

#### *International regulations*

- In the United States (U.S), lidocaine is available in general sale, over the counter (OTC) and prescription medicines. In January 2016, the US Food and Drug Administration (FDA) issued a warning that prescription [oral viscous lidocaine two \(2\) per cent](#) solution should not be used to treat infants and children with teething pain.
- In the United Kingdom (U.K):
  - Lidocaine is available in general sale, OTC and prescription medicines. In December 2018, it was announced that all oral lidocaine-containing products for infant teething are only to be available under the supervision of a pharmacist; and

<sup>131</sup> <https://www.tga.gov.au/publication/required-advisory-statements-medicine-labels-rasml>

<sup>132</sup> <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

<sup>133</sup> <https://portal.apvma.gov.au/pubcris>

- During the period 01 August 2014 to 31 July 2017, patient exposure to amylmetacresol, 2,4-dichlorobenzyl alcohol and lidocaine (XXXXXXXXXXXXXXXXXXXXXXXXXXXX) estimated as XXXXXXXX patients (XXXXXXXX patients exposed to lozenge formulations and XXXXXXX patients exposed to spray formulations). XXXXXXXXXXXXXXXXXXXXXXX holds the marketing authorisation for amylmetacresol, 2,4-dichlorobenzyl alcohol and lidocaine in XX countries. During the reporting period, there has been no marketing authorisation withdrawal, revocation or suspension; no failure to obtain marketing authorisation renewal; no restrictions on distribution; no clinical trial suspension; no dosage modification, no changes in target populations or indications and no formulation changes due to safety reasons.
- In [New Zealand \(Medicines and Medical Devices Safety Authority \(MEDSAFE\)\)](#), lidocaine is available in general sale, OTC and prescription medicines. Lidocaine is classified as general sale in New Zealand in throat sprays containing two (2) per cent or less of lidocaine.
- In Canada, there is [one \(1\) active spray formulation](#) containing lidocaine. It is available OTC at a concentration of 100 mg/mL (ten (10) per cent).

#### *Summary of pre-meeting public submissions*

In response to [the notice published under regulation 42ZCZK](#) advising of the proposed amendment, three (3) submissions were received. One (1) submission supported the amendment and two (2) submissions opposed the amendment.

#### **The main points provided in support of the proposed amendment were:**

- The amendment will allow unscheduled access to lidocaine 0.6% topical aqueous spray. Lidocaine throat lozenges are currently available at higher dose limits without access to health professional advice.
- Lidocaine 0.6% throat spray offers an alternative method of delivery for people who prefer a choice of formulation without having to visit a pharmacy.

#### **The main points provided in opposition to the proposed amendment were:**

- The current scheduling for lidocaine remains appropriate given the potential dangers of this liquid preparation if available outside a pharmacy. As noted in the article '*Lidocaine toxicity*',<sup>134</sup> lidocaine is not without the potential for serious side effects. Applied either by injection, inhalation or as a topical agent to provide anaesthesia, lidocaine has a good safety margin before reaching toxic blood levels. However, since it can be applied in various forms to the same patients, care must be taken to keep track of the total dose given to minimise its systemic toxicity. Lidocaine toxicity not only is determined by the total dose (usually 4.5 mg/kg), but also by the rate of absorption, which is dependent on the blood flow of that tissue.
- There is an assumption that because lidocaine is available in lozenges that it is as safe when it is available as a liquid preparation. Consumers also assume that just because a product is available in a non-pharmacy retail outlet then the product must be safe. However, it is very much easier to overdose with a liquid preparation than it is with a slowly dissolving oral lozenge, especially when considering access by younger children.
- There is greater potential for overdose with a liquid formulation compared to a box of lozenges and it is unlikely that labelling, packaging and presentation would prevent misadventure, especially for young children.
- The use of lidocaine in throat sprays warrant additional vigilance as inadvertent misuse or overuse of topical lidocaine by the general population or use by people with methaemoglobinaemia, even at commonly accepted doses, can have significant negative outcomes. Throat sprays could also be regarded to be more susceptible to unintentional misuse or overuse because of the ease of administration of multiple doses.
- Safe and timely access to medicines is important for consumers. However, a medicine should not be deregulated on the basis that people will be able to choose between different dose forms "without having to visit a pharmacy".

<sup>134</sup> <https://www.ncbi.nlm.nih.gov/books/NBK482479/>

- There are international reports that state that there is a demand for local anaesthetics for use in cutting illegal drugs. In an article by the BBC,<sup>135</sup> *'Mild anaesthetics, found in sunburn and first-aid treatments bought at any chemist, are the latest substances being sought by drug dealers'*. Whilst lidocaine is available in lozenges, one would assume that in a liquid preparation it would be easier

#### Summary of ACMS advice/recommendations to the Delegate

The Committee recommended that the current Schedule 2 entry for lidocaine be amended in the Poisons Standard as follows:

#### Schedule 2 – Amend Entry

LIDOCAINE in preparations for topical use other than eye drops:

- a) containing 10 per cent or less of total local anaesthetic substances, **except**:
  - i) in dermal preparations containing 2 per cent or less of total local anaesthetic substances; or
  - ii) in aqueous sprays for oromucosal use containing 0.6 per cent or less of total local anaesthetic substances; or
- b) in divided preparations containing 200 mg or less of total local anaesthetic substances, **except** in lozenges containing 30 mg or less of total local anaesthetic substances per dosage unit.

The Committee also recommended an implementation date of 1 June 2020.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance.

The reasons for the advice included:

52E(1) Considerations	Reasons
a – the risks and benefits of the use of a substance	<p><i>Risks</i></p> <ul style="list-style-type: none"> <li>Low risk; adverse event reports of lidocaine show small numbers of adverse events. The risk of adverse events is related to the strength lidocaine in a product.</li> </ul> <p><i>Benefits</i></p> <ul style="list-style-type: none"> <li>The proposed scheduling is for a low strength, significantly lower than lidocaine lozenges containing 30 mg or less of total local anaesthetic substances that are currently exempt from scheduling.</li> <li>May be useful for people who would like to avoid lozenges for reasons such as convenience and avoidance of sugar/artificial sweeteners.</li> </ul>
b – the purposes for which a substance is to be used and the extent of use of a substance	<ul style="list-style-type: none"> <li>Lidocaine containing sprays are primarily indicated for relief of painful sore throat. However, the products are registered for additional indications such as mouth and dental ulcers, discomfort associated with tonsillitis and pharyngitis and relief of the symptoms of inflammation.</li> </ul>

<sup>135</sup> <https://www.bbc.com/news/magazine-11177126>

c – the toxicity of a substance	<ul style="list-style-type: none"> <li>· Lidocaine can result in significant toxicity when swallowed and effects are dose dependent.</li> <li>· There have been reports of central nervous system effects, seizures and death in children and adults after ingestion of topical solutions and after use of viscous preparations in the mouth.</li> <li>· However, spray preparations are low strength (0.6% in this case) and the amount delivered per actuation is very small (0.78 mg), which is a factor that mitigates against risk and overdose</li> </ul>
d – the dosage, formulation, labelling, packaging and presentation of a substance	<ul style="list-style-type: none"> <li>· The product is a liquid spray, 20mL container with a directional nozzle. Labelling contains RASML warning statements.</li> <li>· Product is labelled for painful sore throats and is also indicated for other conditions e.g. mouth and oral ulcers, tonsillitis and pharyngitis.</li> </ul>
e – the potential for abuse of a substance	<ul style="list-style-type: none"> <li>· Low potential for abuse or misuse.</li> </ul>
f – any other matters that the Secretary considers necessary to protect public health	<ul style="list-style-type: none"> <li>· Nil.</li> </ul>

#### *Delegate's considerations*

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to lidocaine;
- Advisory Committee on Medicines Scheduling's advice;
- The public submissions received by the [first closing date](#);
- Section 52E of the *Therapeutic Goods Act 1989*, 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 (e) the potential for abuse of a substance;
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- [Scheduling Handbook](#) (V 1.1, July 2019).

#### *Reasons for the interim decision*

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (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 (e) the potential for abuse of a substance.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the Scheduling Factors for Schedule 2.

I have made an interim decision to amend the Schedule 2 entry of lidocaine in the Poisons Standard and I have set out my reasons below.

I am of the view that lidocaine spray products containing up to 0.6 per cent lidocaine does not meet the Scheduling Factors for Schedule 2 and determine that it is able to be supplied, with reasonable safety, without any access to health professional advice. While lidocaine can result in significant

toxicity when swallowed, effects are dose dependent. I have considered that spray products containing up to 0.6 per cent lidocaine have a good safety profile that is comparable to the currently available unscheduled lozenges containing up to 30 mg lidocaine.

I note that two pre-meeting public submissions did not support the scheduling proposal on the basis of concerns that a liquid formulation is more likely to cause misadventure or overdose compared to lozenges, citing the risk of methaemoglobinaemia. However, the adverse effects that have been reported following oral use have involved the administration of solutions of 2 to 4 per cent. On balance, I am persuaded by the fact that an individual taking all actuations of a product containing lidocaine in quick succession would ingest approximately 1.44 g of lidocaine base. This is well within the maximum recommended daily dose for oromucosal uses of 2.4 g lidocaine. As such, I consider the toxicity risk low in this case. Further, the risk of children swallowing the whole contents of the bottle is low due to the packaging. Packaging is a directional nozzle and the product is currently exempted from compliance with [Therapeutic Goods Order No. 95 – Child-resistant packaging requirements for medicines 2017](#).<sup>136</sup>

I also recommend the RASML entry for lozenges be updated to include 'lozenges and oromucosal sprays' to ensure that all labels for oromucosal spray preparations contain the required warning statements regarding hot food and drinks and contraindication against use in children under 6 years.

In making my decision, I acknowledge that while there are risks associated with lidocaine, I recognise that it has a long history of use. Further, given the restrictions on dosage form, route of administration, strength, packaging and warning statements, I am satisfied that there is low potential for abuse or misuse.

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<sup>136</sup> <https://www.legislation.gov.au/Details/F2017L01577>



## 2. Interim decisions on proposed amendments referred to the Advisory Committee on Chemicals Scheduling (ACCS #26, November 2019)

### 2.1. Interim decision in relation to carbon monoxide

#### Interim decision

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

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

##### *Applicant's scheduling proposal and reasons for the proposal*

An application to create new Schedule 7, Schedule 6 and Appendix F entries for carbon monoxide was considered.

The Applicant's proposed amendments to the Poisons Standard were:

##### **Schedule 7 – New Entry**

**CARBON MONOXIDE except when included in Schedule 6.**

##### **Schedule 6 – New Entry**

**CARBON MONOXIDE in pressurised gas canisters or cylinders.**

##### **Appendix F– New entry**

**CARBON MONOXIDE**

Part 1 – Warning Statements: **(Scheduling Committee to consider statements that align with the GHS statements for carbon monoxide)**

Part 2 – Safety Directions – General: **(Scheduling Committee to consider directions that align with the GHS directions for carbon monoxide)**

##### **Appendix J – New Entry**

**CARBON MONOXIDE**

##### **Index – New Entry**

**CARBON MONOXIDE**

**Schedule 7**

**Schedule 6**

**Appendix F**

**Appendix J, Part 2**

The Applicant's main points provided in support of the proposed amendment were as follows:

- Carbon monoxide gas has known potential for misuse.<sup>137</sup> Inhalation of carbon monoxide gas has a high potential for causing harm (including death) without warning as it is colourless and odourless.<sup>138</sup>

<sup>137</sup> Milner, *et al.*, (2017). Access to means of suicide, occupation and the risk of suicide: a national study over 12 years of coronial data, BMC Psychiatry 17(125) <https://doi.org/10.1186/s12888-017-1288-0>

<sup>138</sup> Robertson, B. and Cohn, A., (2014). Think carbon monoxide, Medical Journal of Australia 201 (4), 194. doi: 10.5694/mja14.00417

- Carbon monoxide has a high affinity for haemoglobin (a protein found in red blood cells responsible for transporting oxygen) to form a stable complex of carboxyhaemoglobin (COHb).<sup>139</sup> As carbon monoxide binds to haemoglobin at the same sites as oxygen, but approximately 210 times more tightly, this reduces the ability for red blood cells to carry and deliver oxygen to the body.<sup>140</sup> This lack of oxygen can result in tissue hypoxia and, in serious cases of carbon monoxide poisoning, can lead to organ failure and death.<sup>141</sup>
- A Schedule 6 entry for carbon monoxide has been proposed on the grounds that carbon monoxide meets the toxicity scheduling factors as outlined in the Scheduling Policy Framework<sup>142</sup> as follows:
  - The substance has a moderate to high toxicity, which may cause death or severe injury (including destruction of living tissue) if inhaled, taken internally, or in contact with skin or eyes.
    - § Acute inhalation LC<sub>50</sub> (rat) is between 500 mg/m<sup>3</sup> and 3000 mg/m<sup>3</sup> (4 hours); and
    - § Globally Harmonised System of Classification and Labelling of Chemicals (GHS) category Acute Toxicity Cat 3.
- A Schedule 7 entry for carbon monoxide has also been proposed on the grounds that it meets the scheduling factors as outlined in the Scheduling Policy Framework<sup>143</sup> as follows:
  - The substance has a high health hazard
    - § Carbon monoxide presents a severe hazard from repeated and unprotected use or a significant risk of producing irreversible toxicity, which may involve acute, serious, or chronic health risks or even death if it is inhaled.
  - The dangers of handling the poison are such that special precautions are required in its manufacture, handling or use
    - § The dangers associated with handling carbon monoxide are too hazardous for domestic use or use by untrained persons and warrant restrictions on its availability, possession or use.
  - The substance has a high potential for causing harm
    - § Carbon monoxide should be available only to specialised or authorised users who have the skills necessary to handle it safely. Restrictions on its availability, possession, storage or use may apply.
  - Additional controls over access and training for substances in Schedule 7 may be required through inclusion in Appendix J
    - § An Appendix J listing for carbon monoxide would restrict access to authorised or licenced persons. Carbon monoxide has the potential to cause severe and possible irreversible injury if an individual is exposed to high concentrations or a repeated dose. Limiting access to carbon monoxide could prevent the risk of misuse.
- The Schedule 7 record keeping requirements in Section 5 of the Poisons Standard will also provide a mechanism requiring the details of the order, purchaser and supplier and, depending on jurisdiction implementation, a record of a proof of purchaser authorisation. Under this schedule, the relevant records would be kept for a minimum period of five (5) years.

<sup>139</sup> Ryter, S. W., & Choi, A. M. (2013). Carbon monoxide: present and future indications for a medical gas. The Korean journal of internal medicine, 28(2), 123–140. doi:10.3904/kjim.2013.28.2.123

<sup>140</sup> Berg JM, Tymoczko JL, Stryer L (2011). Biochemistry (7th ed.). New York: W H Freeman. ISBN 978-1-4292-7635-1.

<sup>141</sup> Ryter, S. W., & Choi, A. M. (2013). Carbon monoxide: present and future indications for a medical gas. The Korean journal of internal medicine, 28(2), 123–140. doi:10.3904/kjim.2013.28.2.123

<sup>142</sup> Australian Health Ministers' Advisory Council- Scheduling policy framework for medicines and chemicals: <https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>

<sup>143</sup> Australian Health Ministers' Advisory Council- Scheduling policy framework for medicines and chemicals: <https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>

### *Current scheduling status*

Carbon monoxide is not specifically scheduled in the current Poisons Standard.

### *Scheduling history*

Carbon monoxide is not currently scheduled. However, it has been previously included in Appendix B (substances considered not to require control by scheduling).

In June 1991, the Drugs and Poisons Schedule Standing Committee (DPSSC) made a recommendation to delete the carbon monoxide entry from Appendix B. The Committee noted that carbon monoxide is a toxic gas and should not be classified as exempt from scheduling if it has not been considered.

### **Helium**

Helium was also considered for scheduling in November 2017 by the Joint ACMS-ACCS due to its potential for misuse. The Committee recommended, and the Delegate agreed, that helium did not require scheduling.<sup>144</sup> The Delegate found that there were many legitimate uses for helium, most of which were not related to domestic use in party balloons e.g. industrial, scientific and medical; and that helium was an inert, non-toxic gas and that the risk for helium do not exist unless it is deliberately inhaled resulting in oxygen deprivation leading to asphyxiation. The Delegate stated that correct and legitimate use of helium does not meet the scheduling criteria (SPF 2015).

### *Australian regulations*

- Carbon monoxide is not included on [TGA Database](#).<sup>145</sup>
- Carbon monoxide is not included in any medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#). This includes no prescription and no non-prescription medicines.
- Carbon monoxide is not permitted to be included in listed medicines as it is not included in the current [Therapeutic Goods \(Permissible Ingredients\) Determination No.4 of 2019](#).<sup>146</sup>
- No results were found on the [Prescribing medicines in pregnancy database](#)<sup>147</sup> for carbon monoxide.
- The [Medicines Advisory Statement Specification 2019 \(RASML No. 5\)](#)<sup>148</sup> does not require warning statements pertaining to carbon monoxide as there is no product registered for therapeutic use.
- The [Database of Adverse Event Notifications \(DAEN\)](#)<sup>149</sup> contains no reports of adverse events for products containing carbon monoxide as an active ingredient.
- There is one product that produces carbon monoxide listed on the [Public Chemical Registration Information System Search \(PubCRIS\)](#).<sup>150</sup> The active constituents of this product include sodium nitrate and charcoal. After ignition of the cartridge, it produces the gas carbon monoxide. This product is used to poison foxes.
- The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) undertook a human health tier II assessment in July 2014 on [carbon monoxide](#)<sup>151</sup> as part of their Inventory Multi-tiered Assessment (IMAP) framework.
- Safe Work Australia has listed carbon monoxide in the Hazardous Chemical Information System (HCIS) with the current labelling and packaging requirements:<sup>152</sup>
  - Carbon monoxide is required to be labelled with the signal word DANGER.

<sup>144</sup> TGA (2018). Final decisions amending, or not amending, the current Poisons Standard, April 2018: Helium 2.1 Accessed 25 June 2019 Retrieved at <https://www.tga.gov.au/book-page/21-helium-0>.

<sup>145</sup> <https://www.ebs.tga.gov.au/>

<sup>146</sup> <https://www.legislation.gov.au/Details/F2019L01597>

<sup>147</sup> <https://www.tga.gov.au/prescribing-medicines-pregnancy-database>

<sup>148</sup> <https://www.legislation.gov.au/Details/F2019L00213>

<sup>149</sup> <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

<sup>150</sup> <https://portal.apvma.gov.au/pubcris>

<sup>151</sup> [https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment\\_id=934#cas-A\\_630-08-0](https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=934#cas-A_630-08-0)

<sup>152</sup> Safe Work Australia (2016) Hazardous Chemical Information System (HCIS) Carbon monoxide, Accessed 25 June 2019, Retrieved at <http://hcis.safeworkaustralia.gov.au/HazardousChemical/Details?chemicalID=822>

- Carbon monoxide on the HCIS is under the following hazard categories; Flammable gas – category 1, Gasses under pressure, Reproductive toxicity – category 1A, Acute toxicity – category 3, and Specific target organ toxicity (repeated exposure) – category 1
- Carbon monoxide is also required to have the following warning statements; H220 (Extremely flammable gas), H360D (May damage the unborn child), H331 (Toxic if inhaled), and H372 (Causes damage to organs through prolonged or repeated exposure).
- Pictograms are required on the labels of hazardous chemicals used in the workplace. Carbon monoxide is required to be labelled with the following pictograms<sup>153</sup>: GHS02, GHS04, GHS06, GHS08 (see Figure 1).
- The introduction to [Poisons Standard](#) states:
 

Poisons which are packed and sold solely for industrial, manufacturing, laboratory or dispensary use are exempt from all labelling requirements included in the SUSMP as they are covered by labelling requirements under applicable jurisdictional Work Health and Safety laws, as amended from time to time. Note, however that this exemption does not extend to controls on supply of these poisons.
- State and Territory Legislation may have additional controls on the sale of potentially harmful substances. For example in Queensland, the [Summary Offences Act 2005 Part 2 Offences](#) Section 23<sup>154</sup> can apply to substances such as helium and nitrous oxide, but it does not apply to things the manufacturer intends to be ingested:

### 23 Sale of potentially harmful things

- (1) A seller must not sell a potentially harmful thing to another person if the seller knows or believes, on reasonable grounds, that the other person—
- (a) intends to inhale or ingest the thing; or
  - (b) intends to sell the thing to another person for inhalation or ingestion whether by that person or someone else.

Maximum penalty—

- (a) for a first offence—25 penalty units or 3 months imprisonment; or
  - (b) for a second or later offence—50 penalty units or 1 year's imprisonment.
- (2) For the purposes of the *Anti-Discrimination Act 1991*, section 46, a seller is not to be taken to discriminate against a person only because the seller refuses to sell a potentially harmful thing to the person because of subsection (1).
- (3) In this section—

***potentially harmful thing—***

- (a) means a thing a person may lawfully possess that is or contains a substance that may be harmful to a person if ingested or inhaled; and

***Examples—***

§ glue

§ paint

§ a solvent

- (b) includes methylated spirits; and

- (c) does not include a thing intended by its manufacturer to be inhaled or ingested by a person using it.

<sup>153</sup>Safe Work Australia (2016) Hazardous Chemical Information System (HCIS) Carbon monoxide, Accessed 25 June 2019, Retrieved at <http://hcis.safeworkaustralia.gov.au/HazardousChemical/Details?chemicalID=822>

<sup>154</sup> QLD Summary Offences Act 2005 <https://www.legislation.qld.gov.au/view/pdf/inforce/2013-05-03/act-2005-004>

### *International regulations*

ECHA has published assessments for carbon monoxide. The toxicity assessments provided are in consideration of industrial workers as carbon monoxide is used widely in industrial processes. ECHA has not provided a toxicological summary in regards to the general population. ECHA states 'as the general population will not be exposed, DNEL [Derived No-Effect Level] considered unnecessary'.<sup>155</sup>

ECHA has labelling requirements for carbon monoxide. ECHA states the following warning statements regarding carbon monoxide 'substance is toxic if inhaled, may damage the unborn child, causes damage to organs through prolonged or repeated exposure and is an extremely flammable gas'.<sup>156</sup>

In Canada, the American Conference of Governmental Industrial Hygienists (ACGIH®) recommended the exposure limit for carbon monoxide to be 25 ppm TWA Biological Exposure Index.<sup>157</sup>

The workplace exposure standard (WES) in New Zealand is 25 ppm and the short-term exposure limit (STEL) in Slovak Republic is 35 mg/m<sup>3</sup> or 30 ppm. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) of 25 ppm (29 mg/m<sup>3</sup>) TWA. This value is intended to maintain blood carboxyhaemoglobin (COHb) levels below 3.5 %, to minimise potential for adverse neuro-behavioural changes, and to maintain cardiovascular work and exercise capabilities.<sup>158</sup>

The Safe Work Australia requirements for carbon monoxide are in line with both the ECHA regulations and with the regulations provided on the Canadian Centre for Occupational Health and Safety website.<sup>159,160</sup>

### *Current use in Australia*

Carbon monoxide has many industrial uses in Australia, including<sup>161</sup> (but not limited to):

- Processing aids (including the smoking and colour fixture of some meats);<sup>162</sup>
- Manufacture of chemicals, metal and plastic products, metal surface treatment products, polymers and semiconductors;
- Manufacturing intermediates;
- Sewage treatment;
- Present in fuels, metal surface treatment products, polymers, laboratory chemicals etc.; and
- As a calibration gas.<sup>163</sup>

There is also emerging literature to suggest therapeutic uses for carbon monoxide; clinical trials are currently investigating therapeutic roles.<sup>164</sup>

### *Summary of pre-meeting public submissions*

In response to [the notice published under regulation 42ZCZK](#) advising of the proposed amendment, three (3) submissions were received. One (1) submission supported the amendment and two (2) submissions opposed the amendment.

<sup>155</sup> European Chemicals Agency (ECHA) (2019). Accessed 25 June 2019, Retrieved at <https://echa.europa.eu/registration-dossier/-/registered-dossier/15368/7/1>

<sup>156</sup> European Chemicals Agency (ECHA) (2019). Accessed 25 June 2019, Retrieved at <https://echa.europa.eu/registration-dossier/-/registered-dossier/15368/7/1>

<sup>157</sup> CCOHS (2019). OSH Answers Fact Sheets: Carbon Monoxide Accessed 25 June 2019, Retrieved at [https://www.ccohs.ca/oshanswers/chemicals/chem\\_profiles/carbon\\_monoxide.html](https://www.ccohs.ca/oshanswers/chemicals/chem_profiles/carbon_monoxide.html)

<sup>158</sup> [https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment\\_id=934#cas-A\\_630-08-0](https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=934#cas-A_630-08-0)

<sup>159</sup> Safe Work Australia (2016) Hazardous Chemical Information System (HCIS) Carbon monoxide, Accessed 25 June 2019, Retrieved at <http://hcis.safeworkaustralia.gov.au/HazardousChemical/Details?chemicalID=822>

<sup>160</sup> CCOHS (2019). OSH Answers Fact Sheets: Carbon Monoxide Accessed 25 June 2019, Retrieved at [https://www.ccohs.ca/oshanswers/chemicals/chem\\_profiles/carbon\\_monoxide.html](https://www.ccohs.ca/oshanswers/chemicals/chem_profiles/carbon_monoxide.html)

<sup>161</sup> European Chemicals Agency (ECHA) (2019) *Substance information: Carbon monoxide*, Accessed 23 May 2019, Retrieved at <https://echa.europa.eu/substance-information/-/substanceinfo/100.010.118>

<sup>162</sup> FSANZ (2016). *Australia New Zealand Food Standards Code – Schedule 18 – Processing aids*, Accessed 25 June 2019, Retrieved at <https://www.legislation.gov.au/Details/F2019C00130>

<sup>163</sup> CCOHS (2017). OSH Answers Fact Sheets: Carbon Monoxide Accessed 25 June 2019, Retrieved at [https://www.ccohs.ca/oshanswers/chemicals/chem\\_profiles/carbon\\_monoxide.html](https://www.ccohs.ca/oshanswers/chemicals/chem_profiles/carbon_monoxide.html)

<sup>164</sup> Hess, D. R., (2017). Inhaled Carbon Monoxide: From Toxin to Therapy. *Respiratory Care* 62 (10), 1333-1342. doi:10.4187/respcare.05781

**The main points in support of the proposed amendment were:**

- Since January 2014, NSW PIC has received 185 calls regarding deliberate self-poisoning exposures to carbon monoxide.
- Whilst these calls have involved exposures to carbon monoxide from car exhaust fumes, other motor or generator fumes and charcoal burners (rather than inhalation from carbon monoxide canisters), NSW PIC believes the number of calls received indicates that carbon monoxide continues to be an option for deliberate self-poisoning and they strongly support the proposed scheduling.

**The main points in opposition of the proposed amendment were:**

- The proposal could impose significant trading barriers and regulatory consequences throughout the economy.
- Carbon monoxide is not a product that is supplied to the domestic market. Scheduling is inappropriate or unnecessary.
- Carbon monoxide has legitimate uses for industrial purposes only and the risk management control is legislated by workplace laws.
- Carbon monoxide is present at very low levels in the atmosphere. Under the proposed Schedule 7, there is no cut-off threshold, therefore any product with an atmospheric headspace in its packaging would technically be considered a Dangerous Poison. This has the inadvertent potential to remove a significant proportion of products from the marketplace and must be avoided.
- Common applications for carbon monoxide include:
  - Lung function test – typically 0.3% in a mixture of various other gases, very common;
  - Quench gas for polymerisation reactions (as a kind of ‘safety station’) – pure;
  - Ore analysis for iron mines – pure;
  - Calibration gases – typically 5 ppm through to a few percent. Rarely >5%;
  - Modified Atmosphere Packaging (MAP) in food applications, some customers choose to buy pure and mix-on-site and some prefer the safer option of buying a premix at 5% carbon monoxide;
  - Laser resonator gas mixtures – typically low %; and
  - ‘Bump testing’ use in confined space entry or for industrial hygiene applications – in these circumstances customers typically use products with concentrations ranging from 20ppm through to 1000 ppm.
- XXXXXX has initiated its own product stewardship guidelines that will impose barriers to obtaining the product and the guidelines are currently being implemented by members. The guidelines that XXXXXX members have agreed to implement in relation to carbon monoxide and any gas mixture containing 5% or greater carbon monoxide, will not allow supply without a written end user declaration from the purchaser outlining the intended uses for the product, where the product will be used and delivered to and who the product is intended for.
- The XXXXXX members are also providing training and support to customer service staff to identify when a sale may be suspicious and if the declared use is not legitimate.
- The industry believes that the most effective and efficient means of controlling the access and use of these products is through the consistent implementation of agreed guidelines that consider the risk profile of the product.
- Inclusion in Schedule 7 will add significant cost throughout the industry, on a wide-ranging list of products. Under Schedule 7, simple products that pose no health risk, such as air or oxygen, will have full schedule 7 controls applied.



### Summary of ACCS advice/recommendations to the Delegate

The Committee recommended that on balance, carbon monoxide does not require a schedule listing.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (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 that the Secretary considers necessary to protect public health.

The reasons for the advice included:

52E(1) Considerations	Reasons
a – the risks and benefits of the use of a substance	<p><i>Risks</i></p> <ul style="list-style-type: none"> <li>CO is an odourless, colourless, toxic gas that can cause hypoxic tissue damage and death.</li> <li>The public health risks for CO occur through deliberate misuse.</li> </ul> <p><i>Benefits</i></p> <ul style="list-style-type: none"> <li>CO has a number of legitimate uses, mainly in industrial settings.</li> </ul>
b – the purposes for which a substance is to be used and the extent of use of a substance	<ul style="list-style-type: none"> <li>CO products have a number of industrial uses but are not intended for domestic use.</li> <li>Uses include CO as a processing aid and in the manufacture of chemicals (including formaldehyde and synthetic methanol), metals and plastic products, also as a fuel/fuel additive.</li> </ul>
c – the toxicity of a substance	<ul style="list-style-type: none"> <li>CO binds to haemoglobin with stronger affinity than oxygen.</li> <li>At low concentrations, CO causes mild symptoms like headache, dizziness.</li> <li>At higher concentrations, CO causes loss of consciousness and hypoxic damage to tissues e.g. CNS, cardiovascular system, death.</li> <li>CO is particularly toxic to pregnant women/foetus, people with underlying cardiovascular disease.</li> <li>The toxicity of CO is dose, concentration and duration dependent.</li> </ul>
d – the dosage, formulation, labelling, packaging and presentation of a substance	<ul style="list-style-type: none"> <li>CO is packaged in containers intended only for industrial use and is not sold to the public.</li> </ul>
e – the potential for abuse of a substance	<ul style="list-style-type: none"> <li>There is potential for intentional misuse but measures are in place to prevent public access to CO products.</li> <li>Misuse potential: suicide/homicide through CO inhalation.</li> </ul>
f – any other matters that the Secretary considers necessary to protect public health	<ul style="list-style-type: none"> <li>Industry initiatives to further prevent the accessibility of CO products to the public are supported.</li> <li>Some emerging reports of therapeutic use – if these were established a Schedule 4 entry could be considered.</li> </ul>



### *Delegate's considerations*

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to carbon monoxide;
- Advisory Committee on Chemicals Scheduling's advice;
- Section 52E of the *Therapeutic Goods Act 1989*, 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 Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- [Scheduling Handbook](#) (V 1.1, July 2019).

### *Reasons for interim decision*

I agree with the Committee's finding that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are (a) the risks and benefits of the use of a substance; (b) the purpose 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 that the Secretary considers necessary to protect public health.

In my view, the relevant parts of the SPF 2018 are the Scheduling Factors for Schedules 6 and 7.

I have made an interim decision not to amend the current Poisons Standard in relation to carbon monoxide in the terms stated in the proposal as a balance, carbon monoxide does not require control by Scheduling. I have set out my reasons below.

Carbon monoxide is an odourless, colourless gas that binds to haemoglobin with a stronger affinity than oxygen. Carbon monoxide meets the acute inhalation (LC<sub>50</sub> (rat) of 1489 mg/m<sup>3</sup> is between 500 mg/m<sup>3</sup> and 3000 mg/m<sup>3</sup>, 4-hour exposure) toxicological endpoint and Globally Harmonised System (GHS) of Classification and Labelling of Chemicals category, Acute Toxicity Category 3 under the SPF Schedule 6 Scheduling Factors.

I have taken into account that carbon monoxide meets some of the Schedule 7 Scheduling Factors, including having a high toxicity potential, which may cause death or severe injury (due to hypoxic tissue damage) if inhaled. The toxicity of carbon monoxide is dose, concentration and duration dependent. Furthermore, carbon monoxide has the potential to cause harm and warrants restriction on its availability to specialised or authorised users who have the skills necessary to handle it safely. I acknowledge that carbon monoxide has a known potential for misuse and that evidence of deliberate misuse has been reported in suicide attempts and homicide, but overwhelming from sources other than from cylinders or canisters containing carbon monoxide. I have also considered the original proposal regarding additional controls to access and training for carbon monoxide through inclusion in Appendix J.

Having turned my mind to the toxicological and hazard profiles of carbon monoxide as outlined above, I find that on balance, although carbon monoxide is a hazardous substance that meets some of the Scheduling Factors for Schedules 6 and 7, it does not require a schedule listing on the basis that there are no products where high concentrations of carbon monoxide (in canisters or cylinders) are sold to the public for legitimate domestic uses. Legitimate uses of high concentration carbon monoxide are very specialised, with uses predominately limited to industrial purposes. I find that on balance, the risk of public exposure to carbon monoxide from pressurised canisters or cylinders is very low and is more appropriately regulated by industry controls. Further to this, I note the claims made in the public submissions that industry is currently implementing further controls aimed at preventing public access to carbon monoxide products. Having considered the Committee's advice regarding consultation with the jurisdictions to determine additional controls to limit access to authorised or licenced personnel and mandate training via inclusion in Appendix J, as carbon monoxide does not meet all of the Scheduling Factors for Schedule 7, further consideration around an Appendix J are not relevant at this time.

I note that previous consideration by the Delegate and Committee of another gas (helium) in pressurised gas canisters or cylinders in 2017-2018 (ACCS/ACMS #17), did not result in the scheduling of this substance. While helium's deliberate misuse through inhalation leading to oxygen deprivation and asphyxiation could pose a risk to humans, the substance is actually an inert, non-toxic gas that has many legitimate uses including industrial, scientific and medical uses. In addition, a small amount of helium is available for domestic use. The latter allows for general public to access helium in pressurised gas canisters or cylinders for legitimate reasons e.g. inflation of balloons. On the other hand, while carbon monoxide is NOT an inert, non-toxic gas; it does not have any legitimate uses in domestic settings, and is not accessible by the general public. I agree with the current Committee's view (ACCS #26) that access by the general public to pressurised gases in canisters or cylinders would be a key driver for a substance to be considered for scheduling under the Poisons Standard.

I am satisfied that at this time, carbon monoxide does not meet the requirements for inclusion in the Poisons Standard. The risk profile of carbon monoxide is largely mitigated by other regulations in industry and on balance, as carbon monoxide containing-products are not supplied to the public in the domestic market, public risk exposure is low. I have considered that there are some emerging reports of therapeutic use for carbon monoxide and if these were established, a Schedule 4 entry could be considered in the future.

## 2.2. Interim decision in relation to momfluorothrin

### Interim decision

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

#### Schedule 6 – Amend Entry

MOMFLUOROTHTRIN **except in preparations containing 0.2 per cent or less of momfluorothrin.**

#### Index

**MOMFLUOROTHTRIN**

Schedule 6

#### *Proposed date of effect of the proposed amendment*

1 June 2020

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

##### *Applicant's scheduling proposal and reasons for the proposal*

An application to amend the current Poisons Standard with respect to momfluorothrin was considered. The application proposed to include a cut-off for momfluorothrin in Schedule 6 for preparations containing 0.2 per cent or less.

The Applicant's proposed amendments to the Poisons Standard were:

#### Schedule 6 – Amend Entry

MOMFLUOROTHTRIN **except in preparations containing 0.2 per cent or less of momfluorothrin.**

The Applicant's main points provided in support of the proposed amendment were as follows:

- The proposal is to amend the Schedule 6 entry for momfluorothrin to include a cut-off for preparations containing 0.2 per cent or less of momfluorothrin is consistent with the original consideration for scheduling, when momfluorothrin was included in Schedule 6 without a cut-off. The scheduling delegate's final decision<sup>165</sup> on momfluorothrin, published on the TGA web site on 19 November 2015, noted that it may be possible to consider a lower schedule for products with a low percentage content of momfluorothrin at a later time.
- The data provided with this application supports a lower schedule for products containing momfluorothrin at 0.2 per cent or less, through the evaluation of acute toxicity tests conducted using 0.17% momfluorothrin and 0.33% d-phenothrin. The acute oral toxicity tests on the product were conducted using modern protocols which tested up to 2000 mg/kg bw, with no adverse clinical signs.
- In acute toxicity studies in rats, momfluorothrin was of low acute oral toxicity, low acute dermal toxicity and low acute inhalation toxicity. Momfluorothrin was a slight eye irritant in rabbits, but was not a skin irritant in rabbits or a skin sensitiser in guinea pigs (maximisation test).
- The cut off of 0.2 per cent or less is considered to be supported by the data evaluated by the APVMA, based on the testing results from formulations containing 0.17 per cent momfluorothrin in either a hydrocarbon or water based formulation.

<sup>165</sup> Scheduling delegate's final decisions: ACCS, November 2015 – 2.6 momfluorothrin: <https://www.tga.gov.au/book-page/26-momfluorothrin>

### *Current scheduling status*

Momfluorothrin is currently listed in Schedules 6 of the Poisons Standard as follows:

#### **Schedule 6**

MOMFLUOROTHTRIN.

#### **Index**

**MOMFLUOROTHTRIN**

Schedule 6

### *Scheduling history*

In July 2015, the Advisory Committee on Chemicals Scheduling considered a request from the OCS to create a new entry for momfluorothrin in Schedule 6 of the Poisons Standard, based on an application made to the APVMA to register a new active constituent.

The Committee recommended a new Schedule 6 entry be created for momfluorothrin based on it meeting the acute oral toxicity criteria for inclusion in Schedule 6.

The Delegate's [interim decision](#)<sup>166</sup> published on 1 October 2015, was to include momfluorothrin in Schedule 6. While much of the toxicity profile of momfluorothrin was consistent with the SPF criteria for listing in Schedule 5, the Delegate agreed that the LD<sub>50</sub> in female rats was within the Schedule 6 range. In making the interim decision to include momfluorothrin in Schedule 6, the Delegate noted that it may be possible to consider a lower schedule for products with a low percentage content of momfluorothrin at a later time.

The Delegate made a [final decision](#)<sup>167</sup> on 19 November 2015, confirming the interim decision as no evidence had been received to alter the interim decision.

### *Australian regulations*

- Momfluorothrin is not listed on the [TGA Ingredient Database](#).
- There are no medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#)<sup>168</sup> that contain momfluorothrin as an active ingredient.
- Momfluorothrin is not permitted to be included in listed medicines as it is not included in the current [Therapeutic Goods \(Permissible Ingredients\) Determination No.4 of 2019](#).<sup>169</sup>
- The [Database of Adverse Event Notifications \(DAEN\)](#)<sup>170</sup> contains no reports of adverse events for products containing momfluorothrin as an active ingredient.
- There is only one active constituent approval (XXXXX) for momfluorothrin listed on the APVMA [Public Chemical Registration Information System Search \(PUBCRIS\)](#).<sup>171</sup>

### *International regulations*

- As of 25 July 2019, there are two insecticide products containing momfluorothrin as the sole active ingredient and twelve insecticide products containing momfluorothrin in combination with a second active constituent registered with [Health Canada](#).<sup>172</sup>

<sup>166</sup> Scheduling delegate's interim decisions and invitation for further comment: ACCS/ACMS, October 2015: <https://www.tga.gov.au/book-page/scheduling-proposals-referred-august-2015-meeting-advisory-committee-chemicals-scheduling-15-18#momfl>

<sup>167</sup> Scheduling delegate's final decisions: ACCS, November 2015 – 2.6 momfluorothrin: <https://www.tga.gov.au/book-page/26-momfluorothrin>

<sup>168</sup> ARTG search: <https://tga-search.clients.funnelback.com/s/search.html?query=&collection=tga-artg>

<sup>169</sup> Permissible ingredients determination: <https://www.legislation.gov.au/Details/F2019L01597>

<sup>170</sup> <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

<sup>171</sup> APVMA PUBCRIS search results for momfluorothrin:

[https://portal.apvma.gov.au/pubcris?p\\_auth=8h5z2VaY&p\\_p\\_id=pubcrisportlet\\_WAR\\_pubcrisportlet&p\\_p\\_lifecycle=1&p\\_p\\_state=normal&p\\_p\\_mode=view&p\\_p\\_col\\_id=column-1&p\\_p\\_col\\_pos=2&p\\_p\\_col\\_count=4&pubcrisportlet\\_WAR\\_pubcrisportlet\\_javax.portlet.action=search](https://portal.apvma.gov.au/pubcris?p_auth=8h5z2VaY&p_p_id=pubcrisportlet_WAR_pubcrisportlet&p_p_lifecycle=1&p_p_state=normal&p_p_mode=view&p_p_col_id=column-1&p_p_col_pos=2&p_p_col_count=4&pubcrisportlet_WAR_pubcrisportlet_javax.portlet.action=search)

<sup>172</sup> Health Canada, product listings for momfluorothrin: [http://pr-rp.hc-sc.gc.ca/pi-ip/rba-epa-eng.php?p\\_actv=MOMFLUOROTHTRIN](http://pr-rp.hc-sc.gc.ca/pi-ip/rba-epa-eng.php?p_actv=MOMFLUOROTHTRIN)

- Momfluorothrin was approved by the [US EPA in March 2015](#)<sup>173</sup> for use as an insecticide in indoor and outdoor residential and commercial settings.
- Momfluorothrin was approved for use as a biocide in the [European Union](#)<sup>174</sup> in December 2016 in the European Economic Area (EEA). The [European Chemicals Agency \(ECHA\)](#)<sup>175</sup> hazard classification and labelling for momfluorothrin identifies it as ‘...very toxic to aquatic life, very toxic to aquatic life with long last lasting effects, is harmful if swallowed and may cause damage to organs.’
- Momfluorothrin is not included in the New Zealand (NZ) Environmental Protection Authority’s (EPA) [Inventory of chemicals \(NZIoC\)](#).<sup>176</sup> The NZ EPA released document ‘[Application Form: HS8 Application for whether there are Grounds for a Reassessment of a Hazardous Substance](#)’ on 21 September 2019 noting that momfluorothrin is a synthetic pyrethroid not included in the application to establish grounds for reassessment.

#### Summary of pre-meeting public submissions

No public submissions were received in response to [the notice published under regulation 42ZCZK](#) advising of the proposed amendment.

#### Summary of ACCS advice/recommendations to the Delegate

The Committee recommended that the current Schedule 6 entry for momfluorothrin be amended in the Poisons Standard as follows:

#### **Schedule 6 – Amend Entry**

MOMFLUOROTHRIN **except in preparations containing 0.2 per cent or less of momfluorothrin.**

The Committee also recommended an implementation date of 1 June 2020.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice included:

52E(1) Considerations	Reasons
a – the risks and benefits of the use of a substance	<ul style="list-style-type: none"> <li>• Momfluorothrin and the formulation of the products have some risks, but these are mitigated by the recommendations in the APVMA report, especially labelling.</li> <li>• Public exposure modelling conducted by APVMA suggests that the risks for momfluorothrin are lower than for the accompanying active constituent of d-phenothrin and the risk was not assessed by APVMA for momfluorothrin for that reason. The US EPA has noted that the MOEs for momfluorothrin for all scenarios modelled, ranging from 8,300 to 240,000, are not of concern (EPA’s level of concern (LOC) is an MOE of less than 300).</li> </ul>
b – the purposes for which a substance is to be used and the extent of use of a substance	<ul style="list-style-type: none"> <li>• Products containing 1 g/kg (0.1%) momfluorothrin as one of the active constituents in an aerosol formulation is intended for use as an insecticide (flying and crawling insects) in the home garden environment. Application can be by surface or space spray.</li> </ul>

<sup>173</sup> US Regulations registration decision for momfluorothrin: <https://www.regulations.gov/document?D=EPA-HQ-OPP-2013-0478-0020>

<sup>174</sup> EU Comitology Register (2016):

[https://ec.europa.eu/transparency/regcomitology/index.cfm?do=search.documentdetail&dos\\_id=0&ds\\_id=48095&version=2](https://ec.europa.eu/transparency/regcomitology/index.cfm?do=search.documentdetail&dos_id=0&ds_id=48095&version=2)

<sup>175</sup> ECHA information card for momfluorothrin: <https://www.echa.europa.eu/web/guest/substance-information/-/substanceinfo/100.249.276>

<sup>176</sup> NZ EPA, NZ Inventory of Chemicals: <https://www.epa.govt.nz/database-search/new-zealand-inventory-of-chemicals-nzioc/DatabaseSearchForm/?SiteDatabaseSearchFilters=36&Keyword=pyrethroids&DatabaseType=NZIOC>

	<ul style="list-style-type: none"> <li>• The pattern of exposure is expected to be short (application) to intermediate (post application) term duration.</li> <li>• The presentation as a spray limits the magnitude of exposure.</li> </ul>
c – the toxicity of a substance	<ul style="list-style-type: none"> <li>• Low toxicity at 0.2 %. Low acute toxicity. Systemic toxicity is generally observed at higher dose levels, with rats being the most susceptible species.</li> <li>• No observed genotoxicity or mutagenicity.</li> <li>• Carcinogenic in rats at dose rates approaching or exceeding the maximum tolerated dose. Not carcinogenic in mice.</li> <li>• No reproductive or developmental toxicity, however, there may be a neurotoxic effect in dams.</li> <li>• Mild neurotoxic effect in rats, consistent with other pyrethroids.</li> <li>• No adverse effects reported for humans from the data available.</li> </ul>
d – the dosage, formulation, labelling, packaging and presentation of a substance	<ul style="list-style-type: none"> <li>• The product will be packed in 200-500 g tin plated aerosol cans, packaged in cardboard boxes.</li> <li>• Use of the product according to instructions has been determined to not pose a risk based on the momfluorothrin content.</li> </ul>
e – the potential for abuse of a substance	<ul style="list-style-type: none"> <li>• Nil.</li> </ul>
f – any other matters that the Secretary considers necessary to protect public health	<ul style="list-style-type: none"> <li>• Nil for momfluorothrin.</li> <li>• XX.</li> </ul>

#### *Delegate's considerations*

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to momfluorothrin;
- Advisory Committee on Chemicals Scheduling's advice;
- Section 52E of the *Therapeutic Goods Act 1989*, 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 Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- [Scheduling Handbook](#) (V 1.1, July 2019).

#### *Reasons for the interim decision*

I agree with the Committee's finding that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

In my view, the relevant parts of the SPF 2018 are the Scheduling Factors for Schedules 5 and 6.

I have made a decision to exclude momfluorothrin in concentrations of up to 0.2 per cent from scheduling. In making my decision, I have considered the requirements the Scheduling Factors for Schedule 5 and Schedule 6.



Momfluorothrin is a broad spectrum synthetic pyrethroid currently listed under Schedule 6 of the Poisons Standard. Its mode of action is neurotoxic in insects, interrupting the sodium channels of the insect's nervous system, leading to paralysis and death. The original scheduling application for momfluorothrin in 2015 proposed a Schedule 5 entry. While much of the toxicity profile of momfluorothrin is consistent with the SPF criteria for listing in Schedule 5, at that time the Delegate agreed that the acute oral toxicity in female rats was consistent with the Scheduling Factors for Schedule 6 and this was the critical factor driving the scheduling decision. However, in making the decision to include momfluorothrin in Schedule 6, the Delegate noted that it may be possible to consider a lower schedule for products with a low percentage content of momfluorothrin at a later time.

I note that products containing 1 g/kg (0.1%) momfluorothrin as one of the active constituents in an aerosol formulation are intended for use as an insecticide (flying and crawling insects) in the home garden environment with application via surface or space spray. Having deliberated on whether to implement a cut off of 0.2% to unscheduled or a cut off of 0.2% to Schedule 5, I have determined that the weight of evidence supports the less restrictive cut-off of unscheduled.

Momfluorothrin is not potent in terms of mammalian neurotoxicity and acute toxicity tests conducted using 0.17% momfluorothrin (liquid hydrocarbon-based) and 0.12 % momfluorothrin (water-based) formulations revealed no adverse clinical signs in laboratory animals. The data also supports that momfluorothrin at up to 0.17% is not a skin irritant nor a skin sensitiser. While the data showed that both product formulations were slightly irritating to the eyes, I am satisfied that it was the formulation excipients that were responsible for the irritancy rather than momfluorothrin in this case.

Momfluorothrin is only a slight eye irritant and I am in agreement with the Committee that its dilution within the formulations is sufficient to preclude it from causing irritancy.

While undiluted momfluorothrin has a moderate potential for causing harm (based on the acute oral toxicity in female rats), I am satisfied that the APVMA recommended labelling, which is intended to inform users about the safety measures to apply during handling and use (including safety directions), are also adequate to mitigate the possibility of eye irritancy. Further, the use of products containing up to 0.2% momfluorothrin in accordance with proposed APVMA labelling will not pose a significant risk to users.

## 2.3. Interim decision in relation to tetraniliprole

### Interim decision

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

#### Schedule 5 – New Entry

**TETRANILIPROLE** except in preparations containing 20 per cent or less tetraniliprole.

#### INDEX – New Entry

**TETRANIPROLE**

Schedule 5

#### *Proposed date of effect of the proposed amendment*

1 June 2020

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

##### *Applicant's scheduling proposal and reasons for the proposal*

An application to amend the current Poisons Standard with respect to tetraniliprole was considered.

The application proposed to exclude tetraniliprole from scheduling.

The Applicant's main points provided in support of the proposed amendment are as follows:

- The proposal is to consider a new substance, tetraniliprole, which it is considered does not require control by scheduling, based on sufficient toxicological data being available to recommend a scheduling decision. The data supports that tetraniliprole has low toxicity across the toxicological database and does not appear to present any substantial toxicological hazard. Tetraniliprole has low acute toxicity by the oral, dermal, and inhalational routes. Tetraniliprole is not a skin irritant in rabbits, is a slight eye irritant in rabbits and is slightly positive for skin sensitisation in mice. There is no evidence of neurotoxicity, genotoxicity, carcinogenicity, effects on reproduction or teratogenicity. The toxicity profile of tetraniliprole supports consideration for exemption from scheduling.
- There are no other concerns in relation to the potential health hazard when used according to the proposed draft label. No specialised equipment is required for safe use.

##### *Current scheduling status*

Tetraniliprole is not currently scheduled and has not been previously considered for scheduling. Therefore, a scheduling history is not available. However, there are several diamide insecticides scheduled in the Poisons Standard as follows:

#### Schedule 5

FLUBENDIAMIDE.

CYANTRANILIPROLE.

#### Appendix B, Part 3

Substance	Reason for listing	Area of use
CHLORANTRANILIPROLE	a (Low Toxicity)	1.2 (Insecticide)

## *Scheduling history*

### **Flubendiamide**

In October 2007, the National Drugs and Poisons Schedule Committee (NDPSC) considered the scheduling of flubendiamide. The Committee agreed that the toxicity profile generally aligned with the Schedule 5 criteria (i.e. low acute toxicity, slight eye irritant). A member asserted that the possibility of bioaccumulation was another reason that a Schedule 5 listing would be appropriate. A member noted the extended half-life of flubendiamide in the field could lead to possible human exposure. A member also noted the inability to measure inhalation toxicity for flubendiamide, but asserted that this was expected to be low given the formulation of the product. The Committee generally agreed that no low level cut-off could be set. The Committee decided to include a new entry in Schedule 5 for flubendiamide.

### **Cyantraniliprole**

In February 2013, the chemical scheduling delegate made a delegate only decision to include cyantraniliprole, a new insecticide, in Schedule 5 with no cut-off. The Delegate's reasons for the decision stated that the toxicological profile of cyantraniliprole was well characterised and consistent with either listing in Schedule 5 or exemption from scheduling. The primary reason for considering that a Schedule 5 entry would be more appropriate was the slight eye irritancy observed with technical cyantraniliprole, along with the skin and eye irritancy observed with the proposed products (possibly aggravated by other formulation constituents).

### **Chlorantraniliprole**

In February 2008, the NDPSC considered the scheduling of chlorantraniliprole. A member noted that the only toxicology issue was the eye irritancy, which was at the very low end of 'slight'. The liver effects were not an issue as they were only evident following long exposure at high doses. Therefore, the Committee agreed to include chlorantraniliprole in Appendix B, based on low toxicity.

## *Australian regulations*

- Tetraniliprole is not listed on the [TGA Ingredient Database](#).<sup>177</sup>
- There are no medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#)<sup>178</sup> that contain tetraniliprole as an active ingredient.
- Tetraniliprole is not permitted to be included in listed medicines as it is not included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No.4 of 2019](#).<sup>179</sup>
- There are no adverse events recorded on the [Database of Adverse Event Notifications \(DAEN\)](#).
- There are no products containing tetraniliprole listed on the [Public Chemical Registration Information System Search \(PubCRIS\)](#).<sup>180</sup>

## *International regulations*

- Currently, tetraniliprole is registered in Korea, with registrations under consideration in Chile, Japan, India, Malaysia, Pakistan, Mexico, Canada, New Zealand and the United States of America (USA).
- The [European Chemicals Agency \(ECHA\)](#)<sup>181</sup> has the following hazard and classification labelling statement: *'Warning! According to the classification provided by companies to ECHA in REACH registrations this substance is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects and may cause an allergic skin reaction.'* The properties of concern state: *'A majority of data submitters agree this substance is skin sensitising.'*

<sup>177</sup> <https://www.ebs.tga.gov.au/>

<sup>178</sup> <https://www.tga.gov.au/artg>

<sup>179</sup> <https://www.legislation.gov.au/Details/F2019L01597>

<sup>180</sup> [https://portal.apvma.gov.au/pubcris;jsessionid=T5+FPpthvMRokl5S9WlyTDnF?p\\_auth=8UjIUCE8&p\\_p\\_id=pubcrisportlet\\_WAR\\_pubcrisportlet&p\\_p\\_lifecycle=1&p\\_p\\_state=normal&p\\_p\\_mode=view&p\\_p\\_col\\_id=column-1&p\\_p\\_col\\_pos=2&p\\_p\\_col\\_count=4&pubcrisportlet\\_WAR\\_pubcrisportlet\\_javax.portlet.action=search](https://portal.apvma.gov.au/pubcris;jsessionid=T5+FPpthvMRokl5S9WlyTDnF?p_auth=8UjIUCE8&p_p_id=pubcrisportlet_WAR_pubcrisportlet&p_p_lifecycle=1&p_p_state=normal&p_p_mode=view&p_p_col_id=column-1&p_p_col_pos=2&p_p_col_count=4&pubcrisportlet_WAR_pubcrisportlet_javax.portlet.action=search)

<sup>181</sup> <https://echa.europa.eu/search-for-chemicals>

### Summary of pre-meeting public submissions

No submissions were received response to [the notice published under regulation 42ZCZK](#) advising of the proposed amendment.

### Summary of ACCS advice/recommendations to the Delegate

The Committee recommended that tetraniliprole be included in Schedule 5 of the Poisons Standard as follows:

#### Schedule 5 – New Entry

**TETRANILIPROLE except in preparations containing 20 per cent or less tetraniliprole.**

#### INDEX – New Entry

#### **TETRANIPROLE**

#### Schedule 5

The Committee also recommended an implementation date of 1 June 2020.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice included:

52E(1) Considerations	Reasons
a – the risks and benefits of the use of a substance	<ul style="list-style-type: none"><li>• Tetraniliprole is a new anthranilamide group of insecticides with low mammalian toxicity.</li><li>• It has the potential to replace older pesticide actives with higher mammalian toxicity.</li></ul>
b – the purposes for which a substance is to be used and the extent of use of a substance	<ul style="list-style-type: none"><li>• Current use proposal is for professional use only but it could be used domestically in the future.</li><li>• A low application rate of 300 mL of product (or 60 g of tetraniliprole) per hectare is effective.</li><li>• The intended products contain 200 g/L tetraniliprole.</li></ul>
c – the toxicity of a substance	<ul style="list-style-type: none"><li>• Skin sensitisation of tetraniliprole is consistent with a Schedule 5 classification.</li><li>• Tetraniliprole has low acute toxicity by the oral, dermal and inhalation routes. There is no evidence of neurotoxicity or genotoxicity.</li><li>• Tetraniliprole is not a skin irritant (rabbits). However, it is a slight eye irritant (rabbits).</li><li>• The product under consideration for registration contains tetraniliprole at 20% (w/v). At this concentration it is not considered a skin sensitiser.</li></ul>
d – the dosage, formulation, labelling, packaging and presentation of a substance	<ul style="list-style-type: none"><li>• The product under consideration for registration contains a suspension concentrate formulation.</li><li>• The product under consideration for registration is intended for professional application only. It is not a general consumer product.</li><li>• A low application rate of 300 mL of product (or 60 g of tetraniliprole) per hectare is effective.</li></ul>

e – the potential for abuse of a substance	· Nil.
f – any other matters that the Secretary considers necessary to protect public health	· Nil.

#### *Delegate's considerations*

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to tetraniliprole;
- Advisory Committee on Chemicals Scheduling's advice;
- Section 52E of the *Therapeutic Goods Act 1989*, 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 Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- [Scheduling Handbook](#) (V 1.1, July 2019).

#### *Reasons for interim decision*

I agree with the Committee's finding that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

In my view, the relevant parts of the SPF 2018 are Schedule 5 and Appendix B.

I have made a decision to include tetraniliprole at concentrations of 20 per cent or greater in Schedule 5 of the poisons Standard. In making my decision I have considered the requirements for inclusion of a substance in Appendix B and the Scheduling Factors for Schedule 5.

I have taken into account the toxicological data and hazard profile on tetraniliprole that was provided by the Applicant requesting an exemption from scheduling. However, I am satisfied that the information provided on tetraniliprole does not meet the requirements for inclusion in Appendix B to warrant it being considered exempt from scheduling. The criterion for a substance to be included in Appendix B requires that the substance must not meet the Scheduling Factors for any of the Schedules in the Poisons Standard. Tetraniliprole meets several acute toxicity endpoints under the SPF Schedule 5 Scheduling Factors. Therefore, it unsuitable for an exemption from the scheduling requirements under an Appendix B listing.

I find tetraniliprole to be consistent with the Scheduling Factors for Schedule 5 as it meets the acute oral ( $LD_{50} > 2000$  mg/kg bw), dermal ( $LD_{50} > 2000$  mg/kg bw) and inhalation ( $LC_{50} > 5010$  mg/m<sup>3</sup>, 4-hour exposure) toxicological endpoints and is also a slight eye irritant and is slightly positive for skin sensitisation (GHS skin sensitisation category 1B). The data provided in the application also supports that tetraniliprole presents a low health hazard from repeated use as there is no evidence of neurotoxicity, genotoxicity effects on reproduction or teratogenicity. While there was evidence of neoplastic and non-neoplastic tumours in the reproductive tract in female rats, I agree with the Committee's advice that the carcinogenicity data may not be applicable to humans. Tumours were only seen in those animals that received the highest dose tested XXXXXXXXXXXXXXXXXXXXXXXX, of tumours in this group was only slightly greater than in the control group (i.e. an increase of 1). Further, the females that received the highest dose showed the lower mortality. Furthermore, no carcinogenic effects were seen in mice at the highest dose tested XXXXXXXXXXXXXXXX. While the impact of aging on tumourgenesis cannot not be fully excluded, carcinogenicity is more likely after a life time of exposure and considering the use pattern for tetraniliprole, lifetime exposure is considered to be unlikely.

I have taken into account that tetraniliprole is a new derivative of the anthranilide group of insecticides with low mammalian toxicity which has the potential to replace older pesticide actives with higher mammalian toxicity. A product containing 20 per cent (w/v) intended for professional use has been assessed by the APVMA and, in contrast to the technical grade active, is neither a skin sensitiser (negative for skin sensitisation in mouse LLNA test) nor an eye irritant. I have this taken into consideration together with its low toxicity and hazard profiles; the intended use pattern; the proposed APVMA labelling (which includes First Aid Instructions and Safety Direction to mitigate any potential health risks associated with the use of the formulated product); and the lack of pre-meeting submissions opposing the proposed exclusion from Scheduling, I am satisfied that on balance, the data supports a Schedule 5 entry with a cut-off to unscheduled of 20 per cent.



## 2.4. Interim decision in relation to methiozolin

### Interim decision

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

#### Schedule 5 – New Entry

**METHIOZOLIN.**

#### Index – New Entry

**METHIOZOLIN**

Schedule 5

### *Proposed date of effect of the proposed amendment*

1 June 2020

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

#### *Applicant's scheduling proposal and reasons for the proposal*

An application to amend the current Poisons Standard with respect to methiozolin was considered. The application proposed to create a new Schedule 5 entry for methiozolin.

The Applicant's proposed amendments to the Poisons Standard were:

#### Schedule 5 – New Entry

**METHIOZOLIN.**

#### Index – New Entry

**METHIOZOLIN**

Schedule 5

The Applicant's main points provided in support of the proposed amendments were as follows:

- It is proposed that methiozolin be included in Schedule 5 of the Poisons Standard, based on sufficient toxicological data being available to recommend a scheduling decision.
- The data supports that methiozolin has very low toxicity across the toxicological database and does not appear to present any substantial toxicological hazard. Methiozolin has very low acute toxicity by oral, dermal and inhalational routes.
- Methiozolin is not a skin irritant or sensitiser but causes a slight eye irritation in rabbits. The active was not genotoxic in a battery of *in vivo* and *in vitro* assays. There were no adverse effects on reproduction or development observed. Methiozolin was not neurotoxic in an acute study.
- The product, XXXXXXXXXXXX (containing 250 g/L of methiozolin), has low acute toxicity by the oral, dermal and inhalational routes, is moderately irritating for the skin and eye, but is not a skin sensitiser in guinea pigs by the Buehler method. There are no other concerns in relation to the potential health hazard when used according to the proposed draft label.
- The management of methiozolin toxicological risks would be adequately achieved through a listing in Schedule 5 of the SUSMP with no cut-off or exemptions.

#### *Current scheduling status*

Methiozolin is not specifically scheduled and has not been previously considered for scheduling. Therefore, a scheduling history is not available. However, there is one other isoxazoline herbicide scheduled in the Poisons Standard as follows:

## Schedule 6

### PYROXASULFONE.

#### *Scheduling history*

##### **Pyroxasulfone**

In June 2011, the ACCS first considered pyroxasulfone for scheduling. The scheduling proposal was for a Schedule 7 entry with a cut-off to Schedule 6 for products containing 85 per cent or less pyroxasulfone for pre-emergence herbicidal use.

In September 2011, the Delegate made a decision to create new Schedules 6 and 7 entries for pyroxasulfone. This decision included a cut-off to Schedule 6 from Schedule 7 for water dispersible granule preparations when used as a pre-emergence herbicide. The Delegate made this decision following the recommendation from the ACCS. The ACCS noted that while there were minimal acute toxicity concerns, there were serious repeat dose concerns, noting effects on the cardiac muscle even in short term studies. In addition to the cardiac concerns, there were nerve tissue effects at quite low exposure levels, and developmental neurotoxicity in longer term study. The ACCS also noted that a high margin of exposure (MOE) had been determined by the evaluator. However, the ACCS felt that the severity of the endpoints was such that the ACCS could not ignore the possibility of exposure. The Committee generally agreed that Schedule 7 was appropriate for the pyroxasulfone parent entry.

The ACCS noted that the evaluator had asked for a cut-off to Schedule 6 for products containing 85 per cent or less pyroxasulfone for pre-emergence herbicidal use. The ACCS agreed that the percentage component was unnecessary, particularly as the toxicity difference between the high concentration cut-off and the 100 per cent substance was likely to be minimal.

The ACCS noted that the likely exposure to pyroxasulfone given the use pattern was dermal and via inhalation, and that repeat dermal exposure was the main concern. The ACCS noted that this concern was significant enough to not allow any cut-offs from a Schedule 7 parent entry. However, the ACCS contended that this concern was sufficiently mitigated for water dispersible granule formulations due to their lower absorption potential. The ACCS suggested that this presentation could be the basis for a cut-off to Schedule 6. The ACCS agreed, noting the high MOEs determined by the evaluator for the water dispersible formulations, its minimised exposure potential and the additional risk mitigation measures intended to be implemented by the regulator through labelling.

In March 2013, the ACCS considered a recommendation from the Office of Chemical Safety (OCS) to delete the existing Schedule 7 entry for pyroxasulfone and amend the Schedule 6 entry to a simple entry with no cut-offs. The recommendation was based on the evaluation of new data provided in support of an application for the registration of a water dispersible granule herbicide product containing 850 g/kg pyroxasulfone. The OCS recommendation was based on benign tumours seen in one species (rat) in one sex (male) and observed toxicity to the nervous system at low repeat oral doses (i.e. as the additional data and statistical analyses no longer indicated a concern for the developing foetus and child, with pyroxasulfone subsequently considered to represent a moderate hazard from repeated use and a low risk of producing irreversible toxicity).

The ACCS recommended, and the Delegate agreed, that pyroxasulfone be rescheduled from Schedule 7 to Schedule 6 with no cut-offs.

#### *Australian regulations*

- Methiozolin is not listed on the [TGA Ingredient Database](#).
- There are no medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#)<sup>182</sup> that contain methiozolin as an active ingredient.
- Methiozolin is not permitted to be included in listed medicines as it is not included in the current [Therapeutic Goods \(Permissible Ingredients\) Determination No.4 of 2019](#).<sup>183</sup>

<sup>182</sup> <https://www.tga.gov.au/artg>

<sup>183</sup> <https://www.legislation.gov.au/Details/F2019L01597>

- The [Database of Adverse Event Notifications \(DAEN\)](#)<sup>184</sup> contains no reports of adverse events for products containing methiozolin as an active ingredient.
- There are no products containing methiozolin listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#).<sup>185</sup>

#### *International regulations*

- According to the Applicant, methiozolin is currently registered in Japan and Korea, and is under consideration in the USA.
- Methiozolin is not listed with the [European Chemicals Agency \(ECHA\)](#)<sup>186</sup> and according to the [University of Hertfordshire Pesticide Properties DataBase \(PPDB\)](#),<sup>187</sup> the substance is not currently approved for use in the European Union (EU) under [EU Regulation 1107/2009 \(on the Placing of Plant Protection Products on the Market\)](#).<sup>188</sup>
- While methiozolin is not listed in the [United States Environmental Protection Agency's \(US EPA\) Office of Pesticides Programs](#)<sup>189</sup> as an approved active constituent, it is currently under consideration for registration by the herbicide branch of the [US EPA's Pesticide Registration Division](#).<sup>190</sup>
- Methiozolin is not listed as a registered active ingredient in [Health Canada's Pesticide Product Information Database](#).<sup>191</sup>
- Methiozolin is not included in the [New Zealand EPA's Inventory of Chemicals \(NZIOC\)](#).<sup>192</sup>
- Methiozolin, under the trade names 'XXXXXXXX' and 'XXXXXXXX,' was registered in Korea in April 2010 and in Japan in June 2016, respectively.<sup>193</sup>

#### *Summary of pre-meeting public submissions*

No submissions were received in response to [the notice published under regulation 42ZCZK](#) advising of the proposed amendment.

#### *Summary of ACCS advice/recommendations to the Delegate*

The Committee recommended the Poisons Standard be amended as follows:

#### **Schedule 5 – New Entry**

**METHIOZOLIN.**

#### **Index – New Entry**

**METHIOZOLIN**

#### **Schedule 5**

The Committee also recommended an implementation date of 1 June 2020.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) 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.

<sup>184</sup> <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

<sup>185</sup> <https://portal.apvma.gov.au/pubcris>

<sup>186</sup> <https://echa.europa.eu/search-for-chemicals>

<sup>187</sup> <https://sitem.herts.ac.uk/aeru/ppdb/en/Reports/1649.htm>

<sup>188</sup> [http://www.europarl.europa.eu/RegData/etudes/STUD/2018/615668/EPRS\\_STU%282018%29615668\\_EN.pdf](http://www.europarl.europa.eu/RegData/etudes/STUD/2018/615668/EPRS_STU%282018%29615668_EN.pdf)

<sup>189</sup> <https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1>

<sup>190</sup> <https://www.epa.gov/pesticide-registration/pesticide-registration-division-chemical-list-branch-assignments>

<sup>191</sup> <https://pesticide-registry.canada.ca/en/active-ingredient-search.html>

<sup>192</sup> <https://www.epa.govt.nz/database-search/new-zealand-inventory-of-chemicals-nzioc/DatabaseSearchForm?Keyword=methiozolin&DatabaseType=NZIOC&SiteDatabaseSearchFilters=36>

<sup>193</sup> [http://www.moghu.com/eng/02\\_product/01\\_product.php](http://www.moghu.com/eng/02_product/01_product.php)

The reasons for the advice included:

52E(1) Considerations	Reasons
a – the risks and benefits of the use of a substance	<ul style="list-style-type: none"> <li>• Methiozolin has low acute toxicity by oral, dermal and inhalational routes.</li> <li>• The long-term repeat dose effects of methiozolin are unknown.</li> </ul>
b – the purposes for which a substance is to be used and the extent of use of a substance	<ul style="list-style-type: none"> <li>• Repeat use herbicide treatment of turf possibly including domestic use.</li> <li>• Low persistence reflected in its re-application rate.</li> </ul>
c – the toxicity of a substance	<ul style="list-style-type: none"> <li>• Methiozolin has very low acute toxicity by oral and dermal routes.</li> <li>• Eye irritation is slight.</li> <li>• No lifetime studies in mice and rats were presented for methiozolin. However, there was insufficient evidence to conclude under the conditions of exposure and the toxicity data available that methiozolin is likely to pose a carcinogenic risk to humans.</li> <li>• Methiozolin was not a reproductive or developmental toxin in tested species and was not neurotoxic in an acute study.</li> <li>• Methiozolin was not genotoxic in <i>in vivo</i> and <i>in vitro</i> assays.</li> </ul>
d – the dosage, formulation, labelling, packaging and presentation of a substance	<ul style="list-style-type: none"> <li>• Due to formulation, the proposed product does not have lower toxicity. No cut off concentration is relevant.</li> <li>• The product is expected to be packaged in 500 mL and 1 L high density polyethylene (HDPE) containers.</li> </ul>
e – the potential for abuse of a substance	<ul style="list-style-type: none"> <li>• Nil.</li> </ul>
f – any other matters that the Secretary considers necessary to protect public health	<ul style="list-style-type: none"> <li>• Nil</li> </ul>

#### *Delegate's considerations*

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to methiozolin;
- Advisory Committee on Chemicals Scheduling's advice;
- Section 52E of the *Therapeutic Goods Act 1989*, 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 Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- [Scheduling Handbook](#) (V 1.1, July 2019).

### *Reasons for interim decision*

I agree with the Committee's finding that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use of the substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

In my view, the relevant parts of the SPF 2018 are the Scheduling Factors for Schedule 5 and Schedule 6 and in particular Scheduling Factors 1 (toxicity profile of a substance) and 2 (hazard profile of a substance) for both Schedules.

I am satisfied that the data provided in the application supports inclusion of methiozolin in Schedule 5. The acute toxicity of methiozolin is consistent with the SPF Schedule 5 Scheduling Factors on the basis that it has low acute toxicity by oral and dermal routes ( $LD_{50} > 2000$  mg/kg bw and  $LD_{50} > 2000$  mg/kg bw, respectively), is a slight eye irritant and was not genotoxic in *in vivo* and *in vitro* assays. Additionally, and consistent with a Schedule 5 entry, the hazard profile for methiozolin is considered to be low as it does not exhibit significant reproductive or developmental toxicity and was not found to be neurotoxic in an acute study.

When the Scheduling Factors for Schedules 5 and 6 are considered, I find that while the acute inhalational toxicity for methiozolin is compatible with Schedule 6 at the maximum attainable concentration, I have given more weight to the oral, dermal and eye irritancy having met Schedule 5. I also note that methiozolin is neither a skin irritant nor skin sensitiser and does not meet the Scheduling Factors for inclusion in Schedules 5 or 6.

I note the Committee's concern that there were data gaps in the application on carcinogenicity and irreversible toxicity. Given that the sub-chronic studies in rats and dogs did not show evidence of histopathology/degenerative changes to any organ system and that methiozolin was negative in the genotoxicity studies conducted, I find that there is insufficient evidence to conclude that under the conditions of exposure and the toxicity data available that methiozolin is likely to pose a carcinogenic risk to humans. Consequently, I agree with the Committee recommendation that the absence of this data is insufficient to warrant a Schedule 6 entry.

Taking into consideration that the proposed APVMA labelling will include First Aid Instructions and Safety Direction to mitigate any potential health risks associated with the use of methiozolin and the lack of submissions opposing the proposed the Schedule 5 cut-off entry, I am satisfied that the weight of evidence supports that the management of methiozolin toxicological risks can be achieved through a listing in Schedule 5 of the Poisons Standard with no cut-off or exemptions.

## 2.5. Interim decision in relation to lambda-cyhalothrin

### Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to lambda-cyhalothrin as follows:

#### Schedule 7

LAMBDA-CYHALOTHRIN **except** when included in Schedule 5 or 6.

#### Schedule 6

LAMBDA-CYHALOTHRIN:

- a) in aqueous preparations containing 25 per cent or less of microencapsulated lambda-cyhalothrin; or
- b) in emulsifiable granule formulations containing 25 per cent or less lambda-cyhalothrin; or
- c) in other preparations containing 1.6 per cent or less of microencapsulated lambda-cyhalothrin except when included in Schedule 5

#### Schedule 5 – Amend Entry

LAMBDA-CYHALOTHRIN:

- a) in aqueous preparations containing 1 per cent or less of lambda-cyhalothrin; or
- b) in aqueous preparations containing ~~2.5~~10 per cent or less of microencapsulated lambda-cyhalothrin.

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### *Proposed date of effect of the proposed amendment*

1 June 2020

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

#### *Applicant's scheduling proposal and reasons for the proposal*

An application to amend the current Poisons Standard with respect to lambda-cyhalothrin was considered. The application proposed to amend the Schedule 5 cut-off for aqueous preparations containing microencapsulated lambda-cyhalothrin.

The Applicant's proposed amendments to the Poisons Standard were:

#### Schedule 7

LAMBDA-CYHALOTHRIN **except** when included in Schedule 5 or 6.

#### Schedule 6

LAMBDA-CYHALOTHRIN:

- a) in aqueous preparations containing 25 per cent or less of microencapsulated lambda-cyhalothrin; or
- b) in emulsifiable granule formulations containing 25 per cent or less lambda-cyhalothrin; or

- c) in other preparations containing 1.6 per cent or less of microencapsulated lambda-cyhalothrin except when included in Schedule 5

### **Schedule 5 – Amend Entry**

LAMBDA-CYHALOTHRIN:

- a) in aqueous preparations containing 1 per cent or less of lambda-cyhalothrin; or
- b) in aqueous preparations containing 2.510 per cent or less of microencapsulated lambda-cyhalothrin.

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The Applicant's main points provided in support of the proposed amendment were as follows:

- Based on the product acute toxicity, and providing that adequate warnings and safety directions recommended in the present report are displayed on the product label, the product formulation containing lambda-cyhalothrin meets the Scheduling Policy Framework (2018) criteria for Schedule 5 of the Standard for Uniform Scheduling of Medicines and Poisons (SUSMP). There are no other concerns in relation to the potential health hazard when used according to the proposed draft label. The product is presented in a similar manner to a range of other commonly available insecticidal sprays. No specialised equipment is required for safe use.

### *Current scheduling status*

Lambda-cyhalothrin is currently listed in the Poisons Standard as follows:

### **Schedule 7**

LAMBDA-CYHALOTHRIN **except** when included in Schedule 5 or 6.

### **Schedule 6**

LAMBDA-CYHALOTHRIN:

- a) in aqueous preparations containing 25 per cent or less of microencapsulated lambda-cyhalothrin; or
- b) in emulsifiable granule formulations containing 25 per cent or less lambda-cyhalothrin; or
- c) in other preparations containing 1.6 per cent or less of lambda-cyhalothrin except when included in Schedule 5.

### **Schedule 5**

LAMBDA-CYHALOTHRIN:

- a) in aqueous preparations containing 1 per cent or less of lambda-cyhalothrin; or
- b) in aqueous preparations containing 2.5 per cent or less of microencapsulated lambda-cyhalothrin.

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### *Scheduling history*



In November 1987, the Drugs and Poisons Schedule Committee (DPSC) decided to include first aid and safety directions for lambda-cyhalothrin.

In August 1990, the DPSC decided to include preparations containing 1 per cent or less of lambda-cyhalothrin in Schedule 6 and all other preparations containing lambda-cyhalothrin in Schedule 7, based on the toxicity profile of lambda-cyhalothrin. Toxicity data discussed at this meeting included an oral dosing study in dogs, which revealed be short-lived and non-cumulative dose related neurotoxic effects. In addition, a study in human volunteers devoid of asthma revealed that aerosols of lambda-cyhalothrin elicited some mild reaction in more than 50 per cent of volunteers. A dose response relationship was established for the incidences of smarting and watering of the eyes, sneezing, blocked or runny noses and throat/lung irritation.

In November 1991, the DPSC decided to include aqueous preparations containing 1 per cent or less of lambda-cyhalothrin in Schedule 5. The reason for this decision was that the water-based product containing 1 per cent or less of lambda-cyhalothrin provided it was confined to use by pest control operators through a registration mechanism. The minutes' state that the oral LD<sub>50</sub> for the product in rats was >2000 mg/kg.

In November 1994, the NDPSC considered toxicological data on a microencapsulated aqueous suspensions containing 10 per cent lambda-cyhalothrin. Members noted that technical lambda-cyhalothrin had been demonstrated to have slight skin and eye irritancy and may cause transitory facial numbness in humans. The Committee recommended that because of the potential for moderate skin irritation and temporary facial numbness, and the restriction of its use to professional pest operators that microencapsulated aqueous suspensions containing 2.5 per cent or less of lambda-cyhalothrin be included in Schedule 5.

In August 1999, the NDPSC decided to include microencapsulated preparations containing 25 per cent or less of lambda-cyhalothrin in Schedule 6.

In August 2014, the chemicals scheduling delegate decided to increase the allowed concentration in Schedule 6 from 1.5 to 1.6 per cent to ensure that the product formulation, when expressed in grams per 100 millilitre (as per Part I of the Poisons Standard), is covered by the amended entry.

In October 2017, the chemicals scheduling delegate decided to amend the Schedule 6 entry for lambda-cyhalothrin to include emulsifiable granule formulations containing 25 per cent or less of lambda-cyhalothrin.

In June 2019, the Advisory Committee on Chemicals Scheduling considered a proposal to amend the Schedule 5 entry for lambda-cyhalothrin, to allow up to four per cent or less in aqueous microencapsulated preparations. The 'up and down' method for deriving the acute oral LD<sub>50</sub> toxicity data was considered to be imprecise and the committee recommended that this was insufficient to justify a Schedule 5 entry. The chemicals scheduling delegate made an interim decision not to amend the Schedule 5 entry.

#### *Australian regulations*

- Lambda-cyhalothrin is not listed on the [TGA Ingredient Database](#).
- There are no medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#)<sup>194</sup> that contain lambda-cyhalothrin as an active ingredient.
- Lambda-cyhalothrin is not listed in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2019](#),<sup>195</sup> and is not an excipient or active in any products on the ARTG.
- The [Database of Adverse Event Notifications \(DAEN\)](#)<sup>196</sup> contains no reports of adverse events for products containing lambda-cyhalothrin as an active ingredient.
- As of 31 July 2019, there are 52 products containing Lambda-cyhalothrin listed on the [Public Chemical Registration Information System Search \(PubCRIS\)](#).<sup>197</sup> Of these, 14 are active constituent listings and 39 are end-use products.

<sup>194</sup> ARTG search: <https://tga-search.clients.funnelback.com/s/search.html?query=&collection=tga-artg>

<sup>195</sup> <https://www.legislation.gov.au/Details/F2019L01597>

<sup>196</sup> <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

<sup>197</sup> <https://portal.apvma.gov.au/pubcris>

- There is one adverse report relating to lambda-cyhalothrin in the APVMA's [Adverse Experience Reporting Program annual reports](#)<sup>198</sup> from 1995-2015. The report cited in 2015 included 1 case of malaise, allergy and respiratory problems.

### *International regulations*

#### **USA**

Lambda-cyhalothrin was registered with the US Environmental Protection Agency (US EPA) in 1989 and is registered as a biochemical/conventional chemical. It is a restricted use, broad spectrum insecticide used to control most major aphid, caterpillar and beetle pests on a wide variety of crops and for public health pests such as mosquitoes and cockroaches in non-agricultural settings.

#### **Canada**

Lambda-cyhalothrin is a registered pesticide with Health Canada. There are 22 registered products in Canada containing lambda-cyhalothrin.

Canada [re-evaluated Decision PRVD2017-03 of lambda-cyhalothrin](#) in June 2017. The page states 'Before making a final re-evaluation decision on lambda-cyhalothrin, the PMRA will consider all comments received from the public in response to PRVD2017-03, Lambda-cyhalothrin. The PMRA will then publish a Re-evaluation Decision that will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments'. However, it does not appear that Health Canada have published the Re-evaluation Decision.

#### **UK**

Lambda-cyhalothrin was first approved for use in the UK in 1988 (Advisory Committee on Pesticides, 1988).

#### **EU**

Lambda-cyhalothrin is currently a registered active ingredient with the European Chemicals Agency (ECHA). The ECHA hazard classification for lambda-cyhalothrin is '*Danger! According to the classification provided by companies to ECHA in CLP notifications this substance is fatal if inhaled, is very toxic to aquatic life with long lasting effects, is toxic if swallowed, is toxic in contact with skin and is very toxic to aquatic life.*'

Lambda-cyhalothrin is listed in Annex III – substances predicted as likely to meet criteria for category 1A or 1B carcinogenicity, mutagenicity, or reproductive toxicity.

#### **New Zealand (NZ)**

Lambda-cyhalothrin is currently an [approved chemical with the NZ EPA](#).

### *Summary of pre-meeting public submissions*

No submissions were received response to [the notice published under regulation 42ZCZK](#) advising of the proposed amendment.

### *Summary of ACCS advice/recommendations to the Delegate*

The Committee recommended amending the Schedule 5 entry for lambda-cyhalothrin in the Poisons Standard as follows:

#### **Schedule 5 – Amend Entry**

##### **LAMBDA-CYHALOTHRIN:**

- a) in aqueous preparations containing 1 per cent or less of lambda-cyhalothrin; or
- b) in aqueous preparations containing ~~2.5~~**10** per cent or less of microencapsulated lambda-cyhalothrin.

<sup>198</sup> <https://apvma.gov.au/node/10946>

The Committee also recommended an implementation date of 1 June 2020.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice included:

52E(1) Considerations	Reasons
a – the risks and benefits of the use of a substance	<ul style="list-style-type: none"><li>• The risks relating to lambda-cyhalothrin are mitigated by formulation. However, it is essentially a low toxicity presentation as the microencapsulation of lambda-cyhalothrin is consistent with the Schedule 5 Scheduling Factors.</li></ul>
b – the purposes for which a substance is to be used and the extent of use of a substance	<ul style="list-style-type: none"><li>• Lambda-cyhalothrin is an insecticide intended for professional use in commercial, industrial, public and domestic premises.</li></ul>
c – the toxicity of a substance	<ul style="list-style-type: none"><li>• Lambda-cyhalothrin has low oral and dermal toxicity.</li></ul>
d – the dosage, formulation, labelling, packaging and presentation of a substance	<ul style="list-style-type: none"><li>• Aqueous preparation of microencapsulated lambda-cyhalothrin is to be supplied as a concentrate in containers from 250 mL (bottle) or 50 mL (sachet).</li><li>• Lower package size may be used by a householder.</li></ul>
e – the potential for abuse of a substance	<ul style="list-style-type: none"><li>• Nil.</li></ul>
f – any other matters that the Secretary considers necessary to protect public health	<ul style="list-style-type: none"><li>• Nil</li></ul>

#### *Delegate's considerations*

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to lambda-cyhalothrin;
- Advisory Committee on Chemicals Scheduling's advice;
- Section 52E of the *Therapeutic Goods Act 1989*, 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 Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- [Scheduling Handbook](#) (V 1.1, July 2019).

#### *Reasons for interim decision*

I agree with the Committee's finding that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (b) the purpose 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.

In my view, the relevant parts of the SPF 2018 are the Scheduling Factors for Schedules 5.

- I have taken into consideration the toxicological data on lambda-cyhalothrin provided by the Applicant and have made the decision to increase the cut-off to Schedule 5 from 2.5 per cent to 10 per cent. I am satisfied that on balance, the benefits outweigh any potential public health risks. In making my decision, I have considered the Scheduling Factors for inclusion in Schedule 5. Microencapsulated lambda-cyhalothrin is an insecticide intended for professional use in commercial, industrial, public and domestic premises and has no established therapeutic value in humans. The acute toxicity data for microencapsulated lambda-cyhalothrin are consistent with the SPF Schedule 5 Scheduling Factors, including being a slight eye irritant. However, it is neither a skin irritant nor a skin sensitiser. In considering the toxicity data provided for a formulation containing 10 per cent microencapsulated lambda-cyhalothrin, I am satisfied that it supports a presentation of a low hazard from repeated use and is unlikely to produce irreversible toxicity.
- I have considered the advice from the APVMA regarding the lack of a risk assessment on neurotoxicity and agree with the Committee's recommendation that observed neurotoxic effects are transient and are expected to be equivalent to or no greater than that of the currently registered product which uses similar application rates. Furthermore, no other significant toxicities have been identified (e.g. respiratory sensitisation, mutagenicity, carcinogenicity, reproductive toxicity etc.) supporting that microencapsulated lambda-cyhalothrin at a concentration of 10 per cent or less presents a low potential for causing harm.

While there is a possibility that the smaller pack sizes may be sold to non-professionals for use in domestic settings, the risks associated with it being used contrary to the APVMA-approved directions are no greater than non-compliant professional use. Given that there is no legal mechanism to prevent sale of the smaller pack sizes into the home garden (domestic) market as it relates to the Poison Standard, I have given little weight to the potential availability to domestic users via hardware retailers and/or garden centres in making my decision.

- Taking into consideration that lambda-cyhalothrin is present in a number of registered agricultural products, the proposed use is similar to other commonly available insecticides and its toxicity profile has been well established, I am satisfied that the weight of evidence supports the increase to the Schedule 5 cut-off to 10 per cent. Further, the proposed APVMA labelling (including First Aid Instructions and Safety Direction) will mitigate any potential health risks associated with the use of the product.

### 3. Interim decision on proposed amendment referred to the Advisory Committee on Medicines and Chemicals Scheduling in joint session (Joint ACCS/ACMS #23, November 2019)

#### 3.1. Interim decision in relation to caffeine

##### Interim decision

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

##### Schedule 6 – New Entry

##### CAFFEINE **except:**

- a) when included in Schedule 4; or
- b) in divided preparations for internal human therapeutic use when labelled with a maximum recommended daily dose of no greater than 600 milligrams of total caffeine; or
- c) in undivided preparations for internal human therapeutic use with a concentration of less than 5 per cent of total caffeine and when labelled with a maximum recommended daily dose of no greater than 600 milligrams of total caffeine; or
- d) in preparations for external use; or
- e) in other preparations with a concentration of less than 5 per cent of caffeine.

##### Schedule 4 – New Entry

##### CAFFEINE for internal human therapeutic use **except:**

- a) in divided preparations when labelled with a maximum recommended daily dose of no greater than 600 milligrams of total caffeine; or
- b) in undivided preparations with a concentration of less than 5 per cent of caffeine and when labelled with a maximum recommended daily dose of no greater than 600 milligrams of total caffeine.

##### Index – New Entry

##### CAFFEINE

cross reference: PARACETAMOL, ASPIRIN, SALICYLAMIDE

Schedule 6

Schedule 4

##### *Proposed date of effect of the proposed amendment*

1 June 2020

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

##### *Applicant's scheduling proposal and reasons for the proposal*

An application to amend the Poisons Standard with respect to caffeine was considered.

The Applicant's proposed amendments to the Poisons Standard were:

##### Schedule 6 – New Entry

##### CAFFEINE (CAS No. 58-08-2) **except:**

- a) when included in Schedule 4; or
- b) in divided preparations for internal human therapeutic use when labelled with a maximum recommended daily dose of no greater than 600 milligrams of total caffeine; or
- c) in undivided preparations for internal human therapeutic use with a concentration of 4 per cent or less of total caffeine and when labelled with a maximum recommended daily dose of no greater than 600 milligrams of total caffeine; or
- d) in preparations for external use; or
- e) in other preparations with a concentration of 4 percent or less of caffeine.

#### **Schedule 4 – New Entry**

**CAFFEINE (CAS No. 58-08-2) for internal human therapeutic use **except:****

- a) in divided preparations when labelled with a maximum recommended daily dose of no greater than 600 milligrams of total caffeine; or
- b) in undivided preparations with a concentration of 4 per cent or less of caffeine and when labelled with a maximum recommended daily dose of no greater than 600 milligrams of total caffeine.

#### **Index – New Entry**

**CAFFEINE (CAS No. 58-08-2)**

**cross reference: PARACETAMOL, ASPIRIN, SALICYLAMIDE**

**Schedule 6**

**Schedule 4**

The Applicant's main points provided in support of the proposed amendments were as follows:

- The dietary ingestion of caffeine has led to it being the most widely consumed psychoactive compound worldwide (Cappelletti *et al.*, 2018).<sup>199</sup> Caffeine powder is readily available for sale and consumption on the Australian market via the internet and numerous pure or highly concentrated (>98%) caffeine powders have been advertised for sale online either on Australian websites or international websites that are available to the Australian public.
- A recent fatality associated with inadvertent caffeine overdose suggests the current availability of pure or highly-concentrated caffeine powder presents a risk of poisoning.
- Appropriate labelling and control of all concentrated caffeine products would reduce the risk of inadvertent overdose.
- The toxicity of orally administered caffeine in rats is within the Australian Health Ministers' Advisory Council (AHMAC) Scheduling Policy Framework for Schedule 6. Potentially fatal doses (reported at 5 g) are easily exceeded with the availability of pure or highly-concentrated caffeine products and intentional ingestion of such products will be reduced if labelled as a 'POISON'.
- The Australian Regulatory Guidelines for Over-The-Counter (OTC) Medicines (ARGOM) and the Therapeutic Goods (Permissible Ingredients) Determination specify appropriate restrictions for internal caffeine within the low risk framework of listed medicines and OTC medicines. Internal human therapeutic use outside of these restrictions should be considered for prescription-only scheduling.

#### *Current scheduling status*

Caffeine is not specifically scheduled in the current Poisons Standard. However, caffeine is included in the Schedule 4 aspirin and salicylamide entries and the Schedule 2 paracetamol entry of the Poisons Standard. See **red text** below:

<sup>199</sup> Cappelletti s, Piacentino D, Fineschi V, Frati P, Cipolloni L and Aromatario M (2018): Caffeine-related deaths: manner of deaths and categories at risk. In *Nutrients* 2018, 10, 611

## Schedule 4

### ASPIRIN

- a) when combined with **caffeine**, paracetamol or salicylamide or any derivative of these substances; or
- b) for injection.

## Schedule 4

SALICYLAMIDE when combined with aspirin, **caffeine** or paracetamol or any derivative of these substances.

## Schedule 2

PARACETAMOL for therapeutic use:

- a) 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
- b) in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or
- c) 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
- d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or
- e) 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
- f) 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 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 of 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 20 tablets or capsules,



- (C) compliant 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.

## **Index**

### **ASPIRIN**

cross reference: **CAFFEINE**, PARACETAMOL, SALICYLAMIDE

### **PARACETAMOL**

cross reference: ASPIRIN, IBUPROFEN, METOCLOPRAMIDE, SALICYLAMIDE, **CAFFEINE**

### **SALICYLAMIDE**

cross reference: ASPIRIN, **CAFFEINE**, PARACETAMOL

There is also an entry for food in Appendix A – general exemptions as follows:

## **Appendix A**

### **FOOD except:**

- a) food additives before incorporation into food; or
- b) when used as a means of administering a poison for therapeutic use.

## *Scheduling history*

### **Caffeine as a single active ingredient**

In November 1986, the National Drugs and Poisons Schedule Committee (NDPSC) discussed a letter from the Australian Federation of Consumers Organisations (AFCO) raising a number of concerns including the use of caffeine as an additive in foods and the open sale of XXXXX caffeine tablets. The Committee considered that AFCO had not provided sufficient evidence of a problem with these tablets to warrant scheduling action.

In June 2006, the NDPSC considered the issues of potential misuse of stimulant/alerting caffeine products and the scheduling of single active caffeine following receipt of an inquiry that raised concerns about the misuse and ease of availability of an OTC product (XXXXXXXXXXXX) containing 100 mg caffeine. The NDPSC considered advice from both the Adverse Drug Reactions which had not received any reports of abuse from any caffeine-containing products and the drug Strategy Branch of the Department of Health and Aging that caffeine did not appear to be an issue. Members also noted that:

- i) according to information from the Sports Dieticians Australia website, in January 2004 caffeine had been removed from the 2004 World Anti-Doping Agency (WADA) Prohibited List; and
- ii) FSANZ had established an Expert Working Group to examine the wider aspects of the safety of dietary sources of caffeine.

The Committee agreed that single active caffeine did not warrant scheduling at that time given evidence for long term detrimental or toxic effects from abuse of caffeine was generally lacking and that the Australian Guidelines for Registration of OTC Medicines required all OTC medicines using caffeine as a stimulant or alerting agent to have an adult dose compliant with 'a 100 mg/dose maximum, which may be repeated at 3 hourly intervals. Do not exceed 600 mg in 24 hours.'

### **Caffeine in combination with analgesics**

In the 1960s – 70s in Australia, analgesic combinations containing aspirin, phenacetin (paracetamol from 1975) and caffeine, or aspirin, salicylamide and caffeine were found to be associated with a high risk of analgesic abuse and consequent analgesic nephropathy. Combinations of any two or more of

paracetamol, aspirin, salicylamide, caffeine or any derivatives of these substances were rescheduled from OTC to Prescription Only following a recommendation from the National Health and Medical (NHMRC) Research Council in 1977.

In October 2003, the NDPSC considered a request to include paracetamol + caffeine in Schedule 2. Members agreed that the scheduling of paracetamol + caffeine as Schedule 4 remained appropriate given the inadequate evidence provided to demonstrate that paracetamol + caffeine was safe and also given that caffeine had potential side effects at high doses. The Committee also felt that the stimulating nature of caffeine might encourage excessive use or abuse of these combination products.

In February 2007, the NDPSC considered the scheduling of aspirin compound analgesics containing paracetamol, caffeine or salicylamide. After consideration of all submissions, the Committee agreed that due to the risk of nephrotoxicity, the current Prescription Only scheduling of aspirin when in combination with paracetamol, caffeine or salicylamide remained appropriate. The Committee also agreed to foreshadow the consideration of paracetamol when in combination only with caffeine for the June 2007 NDPSC Meeting as this was an ongoing harmonisation issue with New Zealand which needed to be resolved.

In June 2007, the NDPSC agreed to down-schedule paracetamol + caffeine from Schedule 4 as the indications for use, safety profile and potential for misuse met the Schedule 2 criteria. The Committee was of the opinion that it would be inappropriate to consider paracetamol + caffeine for exemption from scheduling until market experience had been gained with use as a Schedule 2 preparation.

In October 2009, the NDPSC considered a request from the XXXXXXXXXXXXXXXX (XXX) for the Committee to reconsider its June 2007 decision to include paracetamol + caffeine in Schedule 2, on the grounds of potential toxicity of the formulation when used in excess. It was noted that the Committee had undertaken extensive deliberations in June 2007 and the concerns raised by the XXX were also comprehensively reviewed at that time. Consequently, the Committee decided that the scheduling of paracetamol + caffeine remained appropriate.

In November 2014, the Advisory Committee on Medicines Scheduling (ACMS) considered a proposal to amend the Schedule 2 entry to exempt paracetamol when compounded with caffeine, in a powder or granule product containing 1000 mg or less of paracetamol and in tablets or capsules containing 500 mg or less of paracetamol when paracetamol is the only therapeutic active constituent and when supplied in primary packs of not more than 20 tablets/caplets or 10 sachets of powders/granules. The Delegate's [final](#)<sup>200</sup> decision was consistent with the ACMS advice that the scheduling of paracetamol when compounded with caffeine remained appropriate.

#### *Australian regulations*

- On 20 September 2019, a [media release](#)<sup>201</sup> from the Commonwealth Department of Health announced that the Australian Government '*...is taking decisive action towards banning the sale of pure and highly concentrated caffeine food products (including pure caffeine powder) for personal consumption.*'
- The TGA are [currently working on a consultation on sports supplements](#): '*Proposed clarification that certain sports supplements are therapeutic goods*' which is anticipated to be released sometime in October 2019.
- According to the [TGA Ingredient Database](#),<sup>202</sup> caffeine, caffeine citrate, caffeine hydrate and purine alkaloids calculated as caffeine (of *Paullinia cupana*) are included as follows:
  - Caffeine:
    - § is available for use as an active ingredient in: biologicals, export only, listed medicines, over the counter and prescription medicines;
    - § is not available as a homoeopathic ingredient in listed medicines;

<sup>200</sup> <https://www.tga.gov.au/book/part-final-decisions-matters-referred-expert-advisory-committee-11-14#caffe>

<sup>201</sup> <http://healthmedia.cmail20.com/t/ViewEmail/r/617DEDF66F51E8B52540EF23F30FEDED/E9C071402A77FF03F990754F028F0E8F>

<sup>202</sup> <https://www.ebs.tga.gov.au/>

§ is available for use as an excipient ingredient in: biologicals, devices, export only, listed medicines, over the counter and prescription medicines; and

§ is available for use as an equivalent ingredient in: export only, listed medicines.

– Caffeine citrate:

§ is available for use as an active ingredient in: biologicals and prescription medicines;

§ is available for use as an excipient ingredient in: biologicals, devices, and prescription medicines; and

§ is not available for use as an equivalent ingredient in any application.

– Caffeine hydrate:

§ is available for use as an active ingredient in: biologicals and prescription medicines;

§ is available for use as an excipient ingredient in: biologicals, devices and prescription medicines; and

§ is not available for use as an equivalent ingredient in any application.

– Purine alkaloids calculated as caffeine (of *Paullinia cupana*):

§ is not available for use as an active ingredient in any application;

§ is not available for use as an excipient ingredient in any application; and,

§ is available for use as an equivalent ingredient in: export only, over the counter and prescription medicines.

- There are 77 medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](https://www.tga.gov.au/artg)<sup>203</sup> that contain caffeine as an active ingredient. These include two (2) prescription medicines, 27 non-prescription medicines, 47 listed medicines and one (1) export only medicine.

- [Appendix 5 of the Australian Regulatory Guidelines for OTC Medicines \(ARGOM\)](#)<sup>204</sup> limits caffeine in OTC products to a maximum daily dose of 600 mg for adults and children 12 years and over. Further, labels for OTC medicines containing caffeine must carry the following warning statements:

- Limit the use of caffeine-containing products (including tea and coffee) when taking this product. One tablet/capsule contains about the same amount of caffeine as x cups of instant coffee.
- Caffeine may cause sleeplessness if it is taken up to several hours before going to bed.

- The [Prescribing medicines in pregnancy database](https://www.tga.gov.au/prescribing-medicines-pregnancy-database)<sup>205</sup> classifies caffeine as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Caffeine	A	Central Nervous System	CNS stimulants	-
<b>Category A</b> – Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.				

- [The Database of Adverse Event Notifications \(DAEN\)](#)<sup>206</sup> contains 340 reports of adverse events for products containing caffeine as an active ingredient, with 263 cases where there was a single suspected medicine. There was one (1) case where death was a reported outcome.

<sup>203</sup> <https://www.tga.gov.au/artg>

<sup>204</sup> <https://www.tga.gov.au/book-page/c-d#caffeine>

<sup>205</sup> <https://www.tga.gov.au/prescribing-medicines-pregnancy-database>

- As of 9 August 2019 there are three (3) entries for caffeine listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#).<sup>207</sup> Two entries are caffeine active constituent approvals (XXXXXX and XXXXX) and one is for a veterinary medicine (XXXXXX) containing 1.2% caffeine citrate (equivalent to 0.6% caffeine base) in combination with other active constituents for use as a restorative and appetite stimulate.
- There are no warning statements pertaining to caffeine in the [Medicines Advisory Statement Specification 2019 \(RASML No. 2– Schedule 1\)](#).<sup>208</sup>

#### High-moderate risk changes to permissible ingredients – Caffeine

- Following a safety review, [new requirements for caffeine and caffeine-containing ingredients](#)<sup>209</sup> within listed medicines are specified in the [Therapeutic Goods Amendment \(Permissible Ingredients\) Determination \(No. 1\) 2019](#).<sup>210</sup> This was an unincorporated amendment in the [Therapeutic Goods \(Permissible Ingredients\) Determination \(No. 2\) 2019](#). A delay to implementation of these changes was considered likely to pose an imminent or serious safety risk to consumers (see [High-moderate risk changes](#)<sup>211</sup>). As such, the Delegate of the Minister of Health has considered it appropriate to make this change to the Determination commencing 2 September 2019.
- Caffeine as an individual ingredient remains only for oral use and at a maximum daily dose of 100 mg. However, caffeine, when present as a component of other herbal ingredients, will now have dosage restrictions so that the medicine does not provide more than 400 mg total caffeine per day. A maximum dose of 100 mg per three hours will also be required. These limits consider consumption from other sources such as food, and the adverse effects which are seen with caffeine intake exceeding 400 mg/day and more frequent dosing.
- The additional restrictions have been included to be consistent with all caffeine containing ingredients and cover routes of administration where caffeine is present from other ingredients.
- The warning statement (CAFF) has been adjusted to increase consumer awareness of caffeine intake. An additional warning statement of (CAFFPREG) addresses concerns for caffeine use in pregnancy and lactation. Caffeine as an individual ingredient currently has the requirement for a warning statement for 'Adults only'. The same concerns for caffeine intake for children apply to other ingredients containing caffeine and this statement has been applied to all caffeine containing ingredients above 10 mg daily dose.
- For doses greater than 80 mg/day (which equates to a cup of instant coffee), additional warning statements will be required to address specific safety concerns of inadvertent misuse, interactions with other medicines which may lead to increased caffeine plasma levels or interactions between medicines, and potential adverse effects due to high caffeine intake.
- A caffeine concentration of 1% in undivided preparations was considered acceptable given that 30 g (estimated equivalent of a heaped tablespoon) would deliver only 300 mg of caffeine, which sufficiently reduces the likelihood of inadvertent overdose. A concentration of 33% is considered acceptable in divided preparations that do not require the consumer to measure dosage. This is considered to pose a lower risk of inadvertent overdose and is in line with the highest caffeine concentration in existing OTC products.
- The [new requirements for caffeine](#)<sup>212</sup> have been applied to the following ingredients for internal use or oral use application in listed medicines and are specified in the [Therapeutic Goods \(Permissible Ingredients\) Determination \(No. 4\) 2019](#).<sup>213</sup>
  - Caffeine

<sup>206</sup> <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

<sup>207</sup> <https://portal.apvma.gov.au/pubcris>

<sup>208</sup> <https://www.tga.gov.au/publication/required-advisory-statements-medicine-labels-rasml>

<sup>209</sup> <https://www.tga.gov.au/high-moderate-risk-changes-permissible-ingredients-caffeine>

<sup>210</sup> <https://www.legislation.gov.au/Details/F2019L01113>

<sup>211</sup> <https://www.tga.gov.au/changes-permissible-ingredients-determination#often-high>

<sup>212</sup> <https://www.tga.gov.au/high-moderate-risk-changes-permissible-ingredients-caffeine>

<sup>213</sup> <https://www.legislation.gov.au/Details/F2019L01597>

- Cammellia sinensis
- Coffea arabica
- Coffee
- Cola acuminata
- Cola nitida
- Ilex paraguariensis
- Paullinia cupana
- Theobroma cacao
- The following requirements will have immediate effect:
  - Undivided preparations (e.g. bulk powders) must not contain a concentration of total caffeine greater than 4%.
  - Divided preparations (e.g. tablets) must not contain a concentration of total caffeine greater than 33%.
- For the following requirements, sponsors of existing listed medicines will have until March 2021 to bring affected products into compliance while any new listed medicines will need to comply immediately:
  - The maximum recommended daily dose must not provide more than 400mg of total caffeine from all ingredient sources. NOTE: The existing 100mg maximum daily dose limit for caffeine as an individual ingredient still applies.
  - Undivided preparations must not contain a concentration of total caffeine greater than 1%.
  - The maximum recommended dose must not provide more than 100 mg of total caffeine within a 3-hour period.
  - When the maximum recommended daily dose provides greater than 10 mg of total caffeine, the following warning statements are required:
    - § (ADULT) 'Adults only' (or words to that effect).
    - § (CAFF) 'Contains caffeine [state quantity per dosage unit or per mL or per gram of product] total caffeine [per dosage unit or per mL or per gram]. A cup of instant coffee contains approximately 80mg of caffeine.'
    - § (CAFFPREG) 'Caffeine intake more than 200 mg per day is not recommended during pregnancy or breastfeeding.'
  - When the maximum recommended daily dose provides greater than 80 mg of total caffeine, the following warning statements are required:
    - § (CAFFLIMIT) 'Limit the use of caffeine-containing products (including tea and coffee) when taking this product.'
    - § (CAFFCYP) 'Caffeine interacts with the liver enzyme CYP1A2. Consult your health professional before taking with other medicines' (or words to that effect).

#### **Food Standards Australia and New Zealand (FSANZ)**

- According to [FSANZ](http://www.foodstandards.gov.au/consumer/generalissues/Pages/Caffeine.aspx),<sup>214</sup> there is no recognised health-based guidance value, such as an acceptable daily intake (ADI) for caffeine. However, a 2000 literature review conducted by a [FSANZ Working Group on the safety aspects of dietary caffeine](http://www.foodstandards.gov.au/publications/Documents/EWG_Dietary_caffeine.pdf)<sup>215</sup> concluded that based on the available data:
  - enhanced performance and mood effects may be seen at doses of 37.5 mg (0.54 mg/kg bw/day in 70 kg adults);
  - increased anxiety levels can occur in children at doses of 95 mg (3 mg/kg bw/day in children

<sup>214</sup> <http://www.foodstandards.gov.au/consumer/generalissues/Pages/Caffeine.aspx>

<sup>215</sup> [http://www.foodstandards.gov.au/publications/Documents/EWG\\_Dietary\\_caffeine.pdf](http://www.foodstandards.gov.au/publications/Documents/EWG_Dietary_caffeine.pdf)

aged 5-12 years with a mean bodyweight of 32 kg) and at 210 mg in adults (3 mg/kg bw/day in 70 kg adults); and

- caffeine has been reported to reduce the ability to sleep at doses of 100 mg (1.4 mg/kg bw/day in 70 kg adults) at bedtime.
- The [Food Standards Code](#)<sup>216</sup> restricts how much caffeine can be added to cola-type soft drinks and energy drinks. Foods containing added caffeine must also have a statement on the [label](#)<sup>217</sup> stating that the product contains caffeine. In cola-type drinks, the total caffeine content must not exceed 145 mg/kg (36 mg/ 250 mL serve) in the drink as consumed. Formulated caffeinated beverages (including energy drinks) are regulated under [Standard 2.6.4](#)<sup>218</sup> of the Code. Standard 2.6.4 stipulates that the maximum amount of caffeine (in any form) that these products can contain is 320 mg/L and includes [additional labelling requirements](#)<sup>219</sup> advising the products are not suitable for young children, pregnant or lactating women and individuals sensitive to caffeine. 'Energy shots' marketed as dietary supplements or supplemented foods have been found to contain caffeine and other substances in small volumes at concentrations above the limits prescribed in the Code and therefore do not meet the requirements of Standard 2.6.4.
- In June 2014, a Ministerial Policy Guideline on the Regulatory Management of Caffeine in the Food Supply<sup>220</sup> was endorsed. Recommendations were included in the guidance that the regulatory management of caffeine in the food supply should:
  - a) be based on risk analysis ensuring consideration of general population and taking into account vulnerable population groups including children, adolescents, pregnant and lactating women and caffeine sensitive consumers;
  - b) consider exposure to caffeine from all dietary sources; and
  - c) be informed by emerging evidence and the regulation of caffeine in overseas jurisdictions.
- On 10 July 2019, the Minister for Health, the Hon Greg Hunt and the Minister for Aged Care and Senior Australians and Minister for Youth and Sports, Senator the Hon Richard Colbeck asked FSANZ to look into the [safety of caffeine powders and high caffeine content food products](#).<sup>221</sup> The Ministers also asked FSANZ to consider the need for appropriate warning labels and consumer safety information for these products.
- On 30 August 2019, Mark Booth, CEO of FSANZ wrote a [report](#) in response to the request from Ministers Hunt and Colbeck on pure and highly concentrated caffeine products.<sup>222</sup> The report covers the current regulatory framework and permissions for use of caffeine in the Australia New Zealand Food Standards Code; identifies high risk areas where regulation should be strengthened; and, preliminary recommendations regarding the safety of high caffeine products based on consultation with key stakeholders (the report discusses current actions being taken by the TGA (i.e. amendments to the Permissible Ingredients Determination as discussed above and this scheduling application). The report identified that *'the immediate and acute risk is the sale to consumers of pure or highly purified forms of caffeine that require a very small safe dose to be measured from a potentially lethal amount'*.
- On 20 September 2019, [Minister Colbeck released a response](#) to the report and agreed to all recommendations made by FSANZ to enhance consumer safety with regards to caffeine powder and high caffeine content food.<sup>223</sup> The recommendations are as follows:
  - RECOMMENDATION ONE: That FSANZ develop and declare as urgent a proposal to amend the Code to prohibit the retail sale of pure and highly concentrated caffeine food products.

<sup>216</sup> <http://www.foodstandards.gov.au/code/Pages/default.aspx>

<sup>217</sup> <http://www.foodstandards.gov.au/consumer/labelling/advisory/Pages/default.aspx>

<sup>218</sup> <https://www.legislation.gov.au/Series/F2015L00467>

<sup>219</sup> <http://www.foodstandards.gov.au/consumer/labelling/advisory/Pages/default.aspx>

<sup>220</sup> <https://foodregulation.gov.au/internet/fr/publishing.nsf/Content/publication-Policy-Guideline-on-the-Addition-of-Caffeine-to-Foods>

<sup>221</sup> <http://www.foodstandards.gov.au/Pages/Review-of-caffeine.aspx>

<sup>222</sup> <http://www.foodstandards.gov.au/Documents/CaffeineReport2019.pdf>

<sup>223</sup> <https://www.health.gov.au/ministers/senator-the-hon-richard-colbeck/media/australia-to-protect-consumers-by-banning-sale-of-pure-caffeine-powder>



- RECOMMENDATION TWO: That FSANZ consider developing a maximum limit of caffeine in foods, based on the outcomes of the current review of Standard 2.9.4 – Formulated Supplementary Sports Foods.
- RECOMMENDATION THREE: That a coordinated inter-agency consumer information campaign on safe caffeine consumption be developed and implemented in conjunction with the implementation of recommendation one, if adopted.
- RECOMMENDATION FOUR: That, prior to or in parallel with the consumer information campaign, guidance on the regulation of products containing pure or high concentrations of caffeine, and high caffeine content products, be developed by Implementation Subcommittee for Food Regulation (ISFR) for, and agreed by, enforcement agencies to inform compliance action.
- RECOMMENDATION FIVE: That targeted research on caffeine consumption across the Australian and New Zealand population, including consumption by specific vulnerable population groups, continue to be undertaken, including as part of the upcoming Intergenerational Health and Mental Health Study.<sup>224</sup>
- In September 2019, FSANZ also published [a food issues brief for consumers on caffeine](#).<sup>225</sup> Topics covered include caffeine levels in common foods, safe caffeine limits, how caffeine is regulated and what the government is doing about caffeine powders and high caffeine content products.
- In November 2019, FSANZ published an [urgent proposal](#)<sup>226</sup> for public consultation on a proposal to amend the Food Standards Code (the Code) to prohibit the retail sale of pure and highly concentrated caffeine products. [Proposal P1054](#)<sup>227</sup> was prepared after reviewing and reporting to Ministers Hunt and Colbeck on the current availability and regulation of caffeine, and on options for strengthening regulations and consumer warnings in relation to pure and highly concentrated caffeine food products. One of the five recommendations contained in the report to the Ministers was the recommendation that FSANZ, 'develop and declare as urgent a proposal to amend the Code to prohibit the retail sale of pure and highly concentrated caffeine food products.'<sup>228</sup> The draft variation which is the subject of this consultation, proposed to 'prohibit the sale of foods in which total caffeine is present in a concentration of 5% (5 g/100 g) or more, in the product presented at retail sale, unless that sale or presence was expressly permitted by the Code.'<sup>229</sup> The proposed amend to the code would not affect the continued use of caffeine as an ingredient in foods such as formulated caffeinated beverages and cola beverages.

### *International regulations*

- In June 2016, the International Agency for Research on Cancer (IARC), the cancer agency of the World Health Organization (WHO), released the findings of an international Working Group of 23 scientists convened to evaluate the [carcinogenicity of drinking coffee](#)<sup>230</sup> (and hot beverages and maté). The Working Group found no conclusive evidence for a carcinogenic effect of drinking coffee. Consequently, coffee was reclassified from *possibly carcinogenic to humans* (Group 2B) to *not classifiable as to its carcinogenicity to humans* (Group 3).

### **Canada**

- As of 9 August 2019, Health Canada has approved 21 products that contain caffeine<sup>231</sup> for use in humans. All approved medicines are tablets for oral use and are either un-scheduled (1), or scheduled as OTC (15) or narcotic (controlled substances) (8), medicines. The unscheduled preparation contains 200 mg caffeine as the sole active ingredient and is approved for use as a diuretic. The 15 OTC medicines, approved for use as analgesics and antipyretics include caffeine at 15 mg (4), 32 mg (2) and 65 mg (9) in combination with one or more of the following: acetylsalicylic acid, codeine phosphate, acetaminophen (paracetamol) and pyrilamine maleate.

<sup>224</sup> FSANZ review (2019) Pure and highly concentrated caffeine products, p11:

<http://www.foodstandards.gov.au/Documents/CaffeineReport2019.pdf>

<sup>225</sup> <http://www.foodstandards.gov.au/consumer/generalissues/Pages/Caffeine.aspx>

<sup>226</sup> <https://www.foodstandards.gov.au/code/proposals/Pages/P1054.aspx>

<sup>227</sup> <https://www.foodstandards.gov.au/code/proposals/Documents/P1054%20CFS.pdf>

<sup>228</sup> <https://www.foodstandards.gov.au/Documents/CaffeineReport2019.pdf>

<sup>229</sup> <https://www.foodstandards.gov.au/code/proposals/Documents/P1054%20CFS.pdf>

<sup>230</sup> [https://www.iarc.fr/wp-content/uploads/2018/07/pr244\\_E.pdf](https://www.iarc.fr/wp-content/uploads/2018/07/pr244_E.pdf)

<sup>231</sup> <https://health-products.canada.ca/dpd-bdpp/dispatch-repartition.do>



- In Canada, when used in food, [caffeine is regulated as a food additive](#)<sup>232</sup> under the Food and Drugs Regulations and requires a thorough safety assessment by Health Canada before any new uses are permitted. Health Canada's Marketing Authorisations allows for the use of caffeine and caffeine citrate [as food additives](#)<sup>233</sup> in cola-type beverages and non-alcoholic carbonated water-based flavoured sweetened beverages (which includes carbonated soft drinks) to a maximum level of [200 ppm when used singly or in combination with caffeine citrate, 150 ppm, calculate as caffeine](#)<sup>234</sup>, in the finished product, respectively. Caffeinated energy drinks are considered a food and require a Temporary Marketing Authorisation Letter (TMAL) to allow for use of caffeine.
- In October 2018, Health Canada released a [monograph on caffeine in natural health products](#).<sup>235</sup> While not a comprehensive review of the medicinal ingredient, the monograph provides guidance for industry for product licence applications (PLA) and labels for natural health product market authorisations. The monograph discusses routes of administration, dosage forms and doses, indications and contraindications, quantities, directions for use, duration of use, required caution and warning statements and adverse reactions.
- In March 2010, Health Canada released [preliminary guidance for industry on the labelling of caffeine content in pre-packaged foods](#)<sup>236</sup> to encourage food manufacturers to quantitatively label caffeine when present in certain pre-packaged foods such as beverages. In 2012, after a review of caffeine and its potential health effects, Health Canada reconfirmed that for the average adult, moderate daily caffeine intake at dose levels of 400 mg/day is not associated with any adverse effects. However, the data showed that women of childbearing age and children may be at greater risk from caffeine. Consequently, as a precautionary measure, Health Canada released recommended maximum caffeine intake levels for children and women of childbearing age. While there was insufficient data to develop definitive advice for adolescents, Health Canada suggests that daily caffeine intake for this age group be no more than 2.5 mg/kg body weight.<sup>237</sup>

## Europe

- According to the [European Chemicals Agency \(ECHA\)](#)<sup>238</sup>, caffeine is manufactured and/or imported in the European Economic Area (EEA) in 1000 – 100 000 tonnes per year and is used in the manufacture of a range of consumer, professional and industrial products including: cosmetics and personal care products; perfumes and fragrances; laboratory chemicals; pharmaceuticals; washing liquids and detergents; automotive care products; paints and coatings; and as a processing aid in industrial situations. The ECHA recommended hazard classification and labelling statement for caffeine is, 'Warning...this substance is harmful if swallowed.'
- Caffeine, caffeine benzoate, caffeine carboxylic acid, caffeine carboxylol sh-Decapeptide-1, caffeine carboxylol tripeptide-37 and caffeine salicylate are included in the [European Commission \(EU\)'s cosmetic ingredient database \(CosIng\)](#)<sup>239</sup> without restriction, for use in skin conditioning and/or masking products.
- In May 2015, the [European Food Safety Authority \(EFSA\) published its Scientific Opinion on the safety of caffeine](#).<sup>240</sup> The opinion addresses possible adverse health effects of caffeine consumption:
  - from all dietary sources, including food supplements, in the general healthy population and in relevant sub-groups (e.g. children, adolescents, adults, the elderly, pregnant and lactating women and subjects performing physical exercise); and
  - in combination with other substances present in "energy drinks" (D-glucurono-γ-lactone and taurine), alcohol or *p*-synephrine (present in diet products and sports supplements, to

<sup>232</sup> <https://www.canada.ca/en/health-canada/services/food-nutrition/food-safety/food-additives/caffeine-foods/foods.html>

<sup>233</sup> <http://www.inspection.gc.ca/food/requirements-and-guidance/labelling/-f-for-industry/-f-food-additives/eng/1511448488183/1511448488947?chap=6>

<sup>234</sup> <https://www.canada.ca/en/health-canada/services/food-nutrition/food-safety/food-additives/lists-permitted/8-other-accepted-uses.html>

<sup>235</sup> <http://webprod.hc-sc.gc.ca/nhp/nd-bdpsn/atReq.do?atid=caffeine.cafeine&lang=eng>

<sup>236</sup> <https://www.canada.ca/en/health-canada/services/food-nutrition/legislation-guidelines/guidance-documents/preliminary-guidance-industry-labelling-caffeine-content-prepackaged-foods-march-2010.html>

<sup>237</sup> <https://www.canada.ca/en/health-canada/services/food-nutrition/food-safety/food-additives/caffeine-foods/foods.html>

<sup>238</sup> <https://echa.europa.eu/search-for-chemicals>

<sup>239</sup> <https://ec.europa.eu/growth/tools-databases/cosing/index.cfm?fuseaction=search.results>

<sup>240</sup> <https://www.efsa.europa.eu/en/press/news/150527>

determine whether or not these substances modify the possible adverse health effects of caffeine and/or the doses at which such adverse effects may occur.

- Based on available data, [EFSA](#)<sup>241</sup> reached the following conclusions on caffeine intakes which do not give rise to safety concerns:
  - single doses of caffeine up to 200 mg (approximately 3 mg/kg bw for a 70 kg adult) from all sources do not give rise to safety concerns for the general healthy population;
  - caffeine intakes from all sources up to 400 mg (approximately 5.7 mg/kg bw per day for a 70 kg adult) consumed throughout the day do not give rise to safety concerns for health adults in the general population, except for pregnant women;
  - in pregnant women, caffeine intake from all sources up to 200 mg per day consumed throughout the day do not give rise to safety concerns for the developing foetus;
  - single doses of caffeine up to 200 mg and habitual consumption at doses of 200 mg caffeine per day consumed by lactating women do not give rise to safety concerns for the breastfeed infant; and
  - insufficient information was available to derive a safe level of caffeine intake for children and adolescents. However, EFSA proposed that the single dose of caffeine considered to be of no concern for adults (3 mg/kg bw per day) may also be applied to children, as the rate at which children and adolescents process caffeine is at least that of adults, and the studies available on the acute effects of caffeine anxiety and behaviour in children and adolescents support this level.

#### New Zealand

- According to New Zealand's [Medicines and Medical Devices Safety Authority \(Medsafe\)](#),<sup>242</sup> there are twelve (12) products containing [caffeine](#)<sup>243</sup> as the sole ingredient or in combination with other active ingredients (ergotamine, paracetamol, phenylephrine, ascorbic acid, glucose, nicotinic acid, thiamine) currently approved for use. These products are available as prescription only (1), pharmacy only (3) and general sales (8), medicines.
- In August 2019, MedSafe released a consumer up-date on '[Too much caffeine](#)'<sup>244</sup> alerting consumers of the wide variety of products [containing caffeine and to the dangers of over-consumption. The article addresses health risks associated with caffeine over-dose and caffeine withdrawal and advises medical practitioners to question patients presenting with possible symptoms of caffeine overdose about their ingestion of caffeine from less obvious sources \(e.g. dietary supplements, guarana preparations etc.\).](#)

#### United States

- In the United States (US), caffeine and caffeine citrate, either as the sole active ingredient or in combination with other active ingredients (including acetaminophen (paracetamol), aspirin, dihydrocodeine bitartrate, codeine phosphate, butalbital, and ergotamine) are present in a range of OTC (2) and prescription medicines (46) approved by the [US Food & Drug Administration \(FDA\)](#).<sup>245</sup> These drugs are available as tablets and capsules for oral use as solutions for oral and intravenous use and as rectal suppositories.
- Caffeine is included in the [US Code of Federal Regulations \(CFR\)](#)<sup>246</sup> as follows: 'Food and Drugs, Part 340 – Stimulant drug products for over-the-counter (OTC) human use'. When used as an over the counter stimulant drug (i.e. helps to restore mental alertness or wakefulness during fatigue or drowsiness) in a form suitable for oral administration, caffeine is generally considered safe and effective when used within established dosage limits. Products containing caffeine must carry the following warning statements and dosing instructions:

<sup>241</sup> <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2015.4102>

<sup>242</sup> <https://www.medsafe.govt.nz/>

<sup>243</sup> <https://www.medsafe.govt.nz/regulatory/DbSearch.asp>

<sup>244</sup> <https://www.medsafe.govt.nz/profs/PUarticles/caffeine.htm>

<sup>245</sup> <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>

<sup>246</sup> <https://www.ecfr.gov/cgi->

<bin/retrieveECFR?gp=1&SID=8ff94e9d546bdefe9e2a85be7694f7f3&ty=HTML&h=L&mc=true&n=pt21.5.340&r=PART>

### **Warnings:**

- *“The recommended dose of this product contains as much caffeine as a cup of coffee. Limit the use of caffeine-containing medications, foods, or beverages while taking this product because too much caffeine may cause nervousness, irritability, sleeplessness, and, occasionally, rapid heartbeat.”*
- *“For occasional use only. Not intended for use as a substitute for sleep. If fatigue or drowsiness persists or continues to recur, consult a (select one of the following: ‘physician’ or ‘doctor’).”*
- *“Do not give to children under 12 years of age.”*

### **Directions:**

- *“Adults and children 12 years of age and over: Oral dosage is 100 to 200 milligrams not more often than every 3 to 4 hours.”*
- According to the US FDA’s [Food Additive Status List](#),<sup>247</sup> caffeine at 0.02 % in cola-type beverages is generally recognised as safe and is not considered to be a food additive.
- In April 2018, the US FDA released [guidance for industry on highly concentrated caffeine in dietary supplements](#)<sup>248</sup> after products consisting of or containing only pure or highly concentrated caffeine were linked to at least two (2) deaths. Many products that consist of only or primarily pure or highly concentrated caffeine are sold as dietary supplement (powdered and liquid preparations). According to the FDA, the difference between [a safe amount and a toxic or life-threatening amount](#)<sup>249</sup> of caffeine in these highly concentrated products is very small. FDA considers some such products to be adulterated under the *Federal Food, Drug, and Cosmetic Act* (FD&C Act), because they are dietary supplements that present a significant or unreasonable risk of illness or injury under the conditions of use recommended or suggested in the labelling or, if no conditions for use are suggested or recommended, under ordinary conditions of use.
- In April 2018, the US FDA released a [consumer warning](#)<sup>250</sup> about dietary supplements consisting of consisting of pure or highly concentrated caffeine, and recommends avoiding these products. In particular, the FDA is concerned about pure and highly concentrated caffeine, in powdered and liquid forms, sold in bulk containers and marketed directly to consumers, following the deaths related to the use of these products in otherwise healthy individuals. Consumers were advised that pure and highly concentrated caffeine is extremely toxic and that:
  - when encountering pure or highly concentrated caffeinated products they should be aware of the high potency of these products and that parents should be aware that teenagers and young adults may be drawn to these products for their perceived benefits and may not recognise their risks;
  - these products often closely resemble safe household items. Highly concentrated caffeine in a clear liquid form could be easily confused with commonly available liquids, such as water or distilled vinegar, and pure powdered caffeine could be easily confused with flour or powdered sugar and that the consequences of a consumer mistakenly confusing one of these products could be toxic or even lethal;
  - symptoms of caffeine overdose can include rapid or dangerously erratic heartbeat, seizures and death; vomiting, diarrhoea, stupor and disorientation are also symptoms of caffeine toxicity and these symptoms are likely to be much more severe than those resulting from drinking too much coffee, tea or other caffeinated beverages;
  - If consumers believe that they are having an adverse event related to caffeine, stop consuming it and seek immediate medical care or advice.

<sup>247</sup> <https://www.fda.gov/food/food-additives-petitions/food-additive-status-list#ftnC>

<sup>248</sup> <https://www.fda.gov/media/112363/download>

<sup>249</sup> <https://www.fda.gov/food/dietary-supplement-products-ingredients/pure-and-highly-concentrated-caffeine>

<sup>250</sup> <https://wayback.archive-it.org/7993/20190423060402/https://www.fda.gov/Food/DietarySupplements/ProductsIngredients/ucm604315.htm>

- In December 2018, US FDA released another [consumer update](#)<sup>251</sup> on the dangers of over-consumption of caffeine. The FDA estimates toxic effects, such as seizures, can be observed with rapid consumption of around 1200 mg of caffeine, or 0.15 tablespoons of pure caffeine. According to the FDA, the risk of caffeine overdose increases as the concentration of caffeine in the product increases, meaning even small dosages of a highly concentrated product could lead to dangerous effects. Just one teaspoon of pure powdered caffeine can contain the same amount of caffeine as 28 cups of coffee, and a half cup of a liquid highly concentrated caffeine product contains the equivalent of more than 20 cups of coffee. These are toxic amounts that can have serious health consequences, including death. While noting variations in how sensitive people are to the effects of caffeine and how fast they metabolise it, the US FDA [consumer update](#)<sup>252</sup> cites 400 mg caffeine per day (equivalent to 4-5 cups of coffee) as an amount not generally associated with dangerous, negative effects. While the US FDA has not set a level for children, the [American Academy of Paediatrics](#)<sup>253</sup> discourages the consumption of caffeine and other stimulants by children and adolescents.

#### *Summary of pre-meeting public submissions*

In response to the [notice published under regulation 42ZCZK](#) advising of the proposed amendment, three (3) submissions were received. All submissions supported the amendment.

#### **The main points provided in support of the proposed amendment were:**

- Caffeine can cause significant toxicity involving gastrointestinal, stimulant, metabolic and cardiac effects. Exposures of 15-30 mg/kg can cause mild to moderate toxicity and need referral to hospital for monitoring. Caffeine in high concentration preparations poses a greater risk of toxicity and requirement of medical management. A pure caffeine powder could produce toxicity in very small quantities (<1 gm in an adult and as little as 150 mg in a toddler).
- There have been 724 calls to the NSW PIC regarding exposures to caffeine (not energy drinks) since January 2014 and only 1/3 of these calls involved an accidental exposure. This shows wide use/misuse in the community which has remained constant over the last 5 years:

Year	Calls to NSW PIC regarding intentional exposure to caffeine
2014	90
2015	88
2016	88
2017	93
2018	89
2019 to 15 Oct	86

- There have been calls regarding 9 exposures to caffeine powder since 2014 evenly spread over the 5 years. All these patients were symptomatic requiring medical management. Of these exposures, two were deliberate self-harm, two were therapeutic errors and the remaining 5 exposures were intentional exposures for weight-loss, body building or recreational purpose. The inclusion of caffeine powder in Schedule 6 will ensure appropriate labelling and reduce the likelihood of exposures such as these therapeutic errors and intentional misuse.

<sup>251</sup> <https://www.fda.gov/consumers/consumer-updates/spilling-beans-how-much-caffeine-too-much>

<sup>252</sup> <https://www.fda.gov/consumers/consumer-updates/spilling-beans-how-much-caffeine-too-much>

<sup>253</sup> <https://www.aap.org/en-us/about-the-aap/aap-press-room/Pages/Caffeine-Sources-for-Teens-More-Varied-Than-Before.aspx>

- Given the recent fatality associated with inadvertent caffeine overdose, the public submission agreed that the current availability of pure or highly-concentrated caffeine powder presents a risk of poisoning.
- The new proposed Schedule 4 entry will not result in the scheduling of caffeine that occurs naturally in foods or items covered by a Food Standard Code nor will it include stimulant preparations such as XXXXX that are labelled with a maximum recommended daily dose of no more than 600 mg of total caffeine.
- The XXXXXXXXXXXXXXXXXXXXXXXX has no objections to the proposed new Schedule 4 and 6 entries for caffeine.

*Summary of Joint ACCS-ACMS advice/recommendations to the Delegate*

The Committee recommended that caffeine be entered into Schedule 4 and Schedule 6 of the Poisons Standard as follows:

**Schedule 6 – New Entry**

**CAFFEINE except:**

- a) when included in Schedule 4; or
- b) in divided preparations for internal human therapeutic use when labelled with a maximum recommended daily dose of no greater than 600 milligrams of total caffeine; or
- c) in undivided preparations for internal human therapeutic use with a concentration of 5 per cent or less of total caffeine and when labelled with a maximum recommended daily dose of no greater than 600 milligrams of total caffeine; or
- d) in preparations for external use; or
- e) in other preparations with a concentration of 5 percent or less of caffeine.

**Schedule 4 – New Entry**

**CAFFEINE for internal human therapeutic use except:**

- a) in divided preparations when labelled with a maximum recommended daily dose of no greater than 600 milligrams of total caffeine; or
- b) in undivided preparations with a concentration of 5 per cent or less of caffeine and when labelled with a maximum recommended daily dose of no greater than 600 milligrams of total caffeine.

**Index – New Entry**

**CAFFEINE**

cross reference: PARACETAMOL, ASPIRIN, SALICYLAMIDE

Schedule 6

Schedule 4

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice included:

52E(1) Considerations	Reasons
a – the risks and benefits of the use of a substance	<p><i>Risks</i></p> <ul style="list-style-type: none"> <li>• Caffeine is toxic in high doses, not recommended for children and consumption should be limited in pregnancy.</li> <li>• There are approximately 90 calls to NSW PIC annually for caffeine (excluding to energy drinks), with 9 relating to high-concentration caffeine powder.</li> </ul> <p><i>Benefits</i></p> <ul style="list-style-type: none"> <li>• Small amounts of caffeine are widely available in foods and up to 600 mg per day has been safely used as a medicine.</li> <li>• Caffeine is used in combination with analgesia ingredients and a stimulant.</li> </ul>
b – the purposes for which a substance is to be used and the extent of use of a substance	<ul style="list-style-type: none"> <li>• Caffeine is widely consumed as a food ingredient, contained in work-out supplements and available in over-the-counter and prescription products as a stimulant and as an analgesic adjuvant.</li> <li>• High concentration caffeine powders are widely available from internet-based vendors, including from within Australia.</li> </ul>
c – the toxicity of a substance	<ul style="list-style-type: none"> <li>• Doses of up to 400 mg per day of caffeine are not generally considered to be associated with adverse effects. Single doses of 400-600 mg or more can have toxic effects such as vomiting, abdominal pain, and central nervous system symptoms such as agitation, altered conscious state, rigidity and seizures.</li> <li>• There can be cardiovascular effects at high doses of caffeine.</li> <li>• Caffeine exhibits dose dependent toxicity. Acute dose animal toxicity data is consistent with the SPF scheduling factors for Schedule 6. Human poisonings resulting in death have been reported after ingestion of single doses of, on average, 10 grams (5-20 grams).</li> </ul>
d – the dosage, formulation, labelling, packaging and presentation of a substance	<ul style="list-style-type: none"> <li>• High-concentration caffeine powders can deliver a lethal dose with one teaspoon.</li> <li>• It is difficult for a consumer to accurately measure a safe oral dose using high concentration caffeine powder. Caffeine packaged as a medicine with dose restrictions is considered sufficiently safe to remain exempt from scheduling. No evidence has been presented about any safety concerns where caffeine is included in products for external application (cosmetics or personal care products).</li> <li>• There are currently 30 registered medicines containing caffeine on the ARTG including two Schedule 4 (Prescription Only Medicines) for treatment of apnoea in premature infants (up to 32 weeks).</li> </ul>
e – the potential for abuse of a substance	<ul style="list-style-type: none"> <li>• There are currently 30 registered medicines containing caffeine on the ARTG including two Schedule 4 (Prescription Only Medicines) for treatment of apnoea in premature infants (up to 32 weeks).</li> </ul>
f – any other matters that the Secretary considers necessary to protect public health	<ul style="list-style-type: none"> <li>• Amendments to the food standards in parallel with this scheduling amendment are intended to prohibit high concentration caffeine food products.</li> </ul>



### *Delegate's considerations*

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to caffeine;
- Joint Meeting of the Advisory Committee on Chemicals Scheduling and the Advisory Committee on Medicines Scheduling's advice;
- The public submissions made pursuant to regulation 42ZCZK by the [first closing date](#).
- Section 52E of the *Therapeutic Goods Act 1989*, 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 that the Secretary considers necessary to protect public health;
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018);
- [Scheduling Handbook](#) (V 1.1, July 2019);
- The [new requirements for caffeine](#)<sup>254</sup> for internal use or oral use application in listed medicines as specified in the [Therapeutic Goods \(Permissible Ingredients\) Determination \(No. 4\) 2019](#);<sup>255</sup> and
- Food Standards Australia New Zealand's (FSANZ) proposed amendments to the Food Standards Code [to prohibit the retail sale of pure and highly concentrated caffeine food products](#).<sup>256</sup>

### *Reasons for interim decision*

I agree with the Joint ACMS-ACCS #23 (the Committee) findings that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and 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 that the Secretary considers necessary to protect public health.

In my view, the relevant parts of the SPF 2018 are the Scheduling Factors for Schedules 4, 6 and 7.

I have considered the information provided with the application and the advice of the Committee and have made the decision to include caffeine in Schedule 4 and Schedule 6 of the Poisons Standard.

Caffeine is naturally present in various plant-based foodstuffs such as tea, coffee and chocolate. Purified caffeine is also added to a range of products such as cola-type and energy drinks and pre-workout supplements. Therapeutically, caffeine is used as stimulant, an analgesic adjuvant (it augments the analgesic effects of pain relievers such as paracetamol) and is an Australian Pesticides and Veterinary Medicines Authority (APVMA) approved oral veterinary medicine. While caffeine in food and beverages and its use therapeutically is subject to regulatory oversight, pure and highly concentrated caffeine powder, which is not packaged or labelled in a way to reduce the risk of poisoning, can be purchased in Australia without restriction via web-based vendors. The inquest by the Coroner's Court of NSW into a recent fatality associated with inadvertent caffeine overdose, demonstrates that the current availability of pure and highly-concentrated caffeine powder presents a clear public health risk. Given that caffeine is so ubiquitous and is the most widely consumed psychoactive compound worldwide, it was important that I consider any unintended impacts with the proposed scheduling of this substance.

Caffeine exhibits dose dependent toxicity, with pure and highly concentrated caffeine (>98 %) having a moderate to high toxicity, which may cause death or severe injury if taken internally. Seizures can occur with doses of 1200 mg and while a lethal dose is generally considered to be between 5 and 10 g, death has been reported after a single dose of 3 g caffeine, supporting the need to limit access high-

<sup>254</sup> <https://www.tga.gov.au/high-moderate-risk-changes-permissible-ingredients-caffeine>

<sup>255</sup> <https://www.legislation.gov.au/Details/F2019L01597>

<sup>256</sup> <https://www.foodstandards.gov.au/code/proposals/Pages/P1054.aspx>

potency products. A single dose exceeding 400-600 mg has the potential to cause adverse effects such as tachycardia, palpitations, insomnia, restlessness, nervousness, tremor, headache, abdominal pain, nausea, vomiting, diarrhoea and diuresis. The acute oral LD<sub>50</sub> (rat) of 367 mg/kg bw is within the range for the SPF Scheduling Factors for Schedule 6 (i.e. 50 mg/kg – 2000 mg/kg) and potentially fatal doses (reported at 5 g) are easily exceeded with the availability of pure or highly concentrated caffeine products. While pure or highly concentrated caffeine poses a clear public health risk, it does not meet the SPF Scheduling Factors for inclusion in Schedule 7. However, I am satisfied that reasonably foreseeable harm to users from the known dangers of pure and/or highly concentrated caffeine can be sufficiently reduced via a Schedule 6 listing, requiring products to include strong label warnings (i.e. POISON) and extensive safety directions educating consumers on its potential dangers and safe use.

Caffeine is currently included within registered and listed medicines on the Australian Register of Therapeutic Goods (ARTG). The Australian Regulatory Guidelines for Over-The-Counter (OTC) Medicines (ARGOM)<sup>257</sup> and the Therapeutic Goods (Permissible Ingredients) Determination<sup>258</sup> specify appropriate restrictions for internal caffeine within the low risk framework of listed medicines and OTC medicines. Given the toxic effects of increasing doses of caffeine, it is my view that the weight of evidence supports the contention that internal human therapeutic use outside of these restrictions should be Prescription Only Medicines (i.e. Schedule 4). Taking into consideration the widespread dietary consumption of caffeine and caffeine containing products, there is an increased risk of inadvertent caffeine overdose associated with internal therapeutic caffeine use. Given the potential seriousness of adverse health effects, I am of the view that medical oversight is required to minimise the risk associated with caffeine's therapeutic use outside listed and OTC medicines.

While lethal consequences have been observed following inappropriate use of products containing high-concentrations of caffeine, the widespread ingestion of food products containing caffeine indicates appropriate concentration limits need to be specified so that these and other legitimate uses are not inadvertently captured by the proposed Schedule 4 and Schedule 6 entries. In determining a suitable concentration cut-off from Schedule 6, I have considered the Applicant's evidence in support of 4 per cent or less. However, the recent FSANZ review of pure and highly concentrated caffeine products<sup>259</sup> has determined that products containing less than 5 per cent caffeine will not pose an unacceptably high acute risk to consumers. Also, given that the Foods Standard Code and the Poisons Standard sit side-by-side and do not operate in isolation, I have decided that the proposed scheduling cut-off of 4 per cent be changed to less than 5 per cent to align with planned amendments to the Food Standard Code. Furthermore, the proposed Schedule 6 exemption for 'other preparations with a concentration of less than 5 per cent of caffeine' will mean that the single oral veterinary product (containing 6 g/L caffeine (as 12 g/L caffeine citrate)) that is currently available will not be inadvertently captured in Schedule 6 because the caffeine concentration is well below the cut-off (i.e. up to 0.6% concentration).

In light of standard doses of caffeine in food and therapeutic products, I am also satisfied that the 600 mg maximum daily dose exemptions from Schedule 4 and Schedule 6 for preparations for human internal therapeutic use are acceptable. These will continue to allow both ARTG listed and registered products to continue to be marketed without any scheduling restrictions. Although the 600 mg cut-off is higher than the dietary 400 mg recommended by FSANZ which was based on figures from the European Food Safety Authority (EFSA) from 2015<sup>260</sup>, I am of the opinion that it is reasonable given that caffeine is being used as a medicine. Furthermore, the Australian Regulatory Guidelines for OTC Medicines (ARGOM) includes a 100 mg maximum dose and a 600 mg maximum daily dose recommendation (for adults and children over 12 years) for registered over-the-counter products. Following a safety review by the TGA, the Therapeutic Goods Amendment (Permissible Ingredients) Determination (No. 4) 2019<sup>261</sup> now also specifies new requirements for caffeine, including label warning statements and limitations on caffeine concentrations in both divided and undivided medicines for caffeine and caffeine-containing ingredients within listed medicines. Together, I am satisfied that these requirements will help to ensure the safe and quality use of these medicines.

<sup>257</sup> <https://www.tga.gov.au/book-page/c-d#caffeine>

<sup>258</sup> <https://www.legislation.gov.au/Details/F2019L01597>

<sup>259</sup> FSANZ review 2019: Pure and highly concentrated caffeine products: <https://www.foodstandards.gov.au/Documents/CaffeineReport2019.pdf>

<sup>260</sup> EFSA Scientific Opinion on the safety of caffeine (2015): <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2015.4102>

<sup>261</sup> <https://www.legislation.gov.au/Details/F2019L01597>

Caffeine is also widely used in cosmetics and personal care products, primarily for its hydrophilic and possible antioxidant properties. It is listed in the European Union Cosmetic Ingredients database with no restriction on concentration or type of cosmetic products in which it can be used. Given the lack of safety signals, I am satisfied that the exemption from Schedule 6 for preparations for external use will ensure no capture of cosmetic and personal care products containing caffeine. However, the scheduling will still capture high concentration caffeine before it is added to a cosmetic or personal care product, which I consider is appropriate.

### 3.2. Interim decision in relation to *N*-methyl-2-pyrrolidone (NMP)

#### Interim decision

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

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

#### *Applicant's original scheduling proposal and reasons for the proposal*

An application to amend the Poisons Standard with respect to NMP was considered.

The Applicant's proposed amendments to the Poisons Standard were:

#### **Schedule 6 – Amend Entry**

*N*-METHYL-2-PYRROLIDONE **except:**

- a) when included in Schedule 5; or
- b) in cosmetic preparations containing less than 2 per cent of the chemical; or
- c) in preparations **not for cosmetic use** containing 25 per cent or less of designated solvents.

The Applicant's main points provided in support of the proposed amendments were as follows:

- the chemical has reported uses in cosmetic products available for sale in Australia;
- the chemical is expected to be readily absorbed through the skin;
- data from a quantitative risk assessment indicate that cosmetic uses at concentrations above 2 % may pose an unreasonable risk to the public;
- the chemical is prohibited for use in cosmetics in EU;
- the chemical is listed REACH Annex XVII which restricts the use of NMP in consumer applications to <0.3 %; and
- the chemical is classified as hazardous with the following risk phrases for human health in the Hazardous Chemical Information System (HCIS): Eye irritation – category 2A; Skin irritation – category 2; Specific target organ toxicity (single exposure) – category 3 and Reproductive toxicity – category 1B.

#### *Current scheduling status*

*N*-methyl-2-pyrrolidone is currently listed in Part 1, Schedules 5 and 6 and Appendix E, Part 2 of the Poison Standard as follows:

#### **Part 1 – Interpretation**

**“Designated solvent”** means the following:

...

*N*-methyl-2-pyrrolidone

...

#### **Schedule 6**

*N*-METHYL-2-PYRROLIDONE **except:**

- a) when included in Schedule 5; or
- b) in preparations containing 25 per cent or less of designated solvents.

## Schedule 5

### *N*-METHYL-2-PYRROLIDONE:

- a) when packed in single use containers having a capacity of 2 mL or less; or
- b) in preparations containing 50 per cent or less of *N*-methyl-2-pyrrolidone or preparations containing 50 per cent or less of a mixture of any two or more of *N*-methyl-2-pyrrolidone, *N*-(*N*-octyl)-2-pyrrolidone or *N*-(*N*-dodecyl)-2-pyrrolidone **except** in preparations containing 25 per cent or less of designated solvents.

## Appendix E, Part 2

Poison	Standard statements
<i>N</i> -METHYL-2-PYRROLIDONE	
<ul style="list-style-type: none"><li>when included in Schedule 5</li></ul>	<p><b>A:</b> For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once).</p> <p><b>G3:</b> If swallowed, do NOT induce vomiting.</p> <p><b>E1:</b> If in eyes wash out immediately with water.</p>
<ul style="list-style-type: none"><li>when included in Schedule 6</li></ul>	<p><b>A:</b> For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once).</p> <p><b>G3:</b> If swallowed, do NOT induce vomiting.</p> <p><b>E2:</b> If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, for at least 15 minutes.</p>

## Index

### *N*-METHYL-2-PYRROLIDONE

Schedule 6

Schedule 5

Appendix E, Part 2

*N*-methyl-2-pyrrolidone is also cross referenced in the Schedule 5 and index entries for *N*-(*N*-dodecyl)-2-pyrrolidone, as highlighted in the **red text** below:

## Schedule 5

*N*-(*N*-DODECYL)-2-PYRROLIDONE in preparations containing 50 per cent or less of *N*-(*N*-dodecyl)-2-pyrrolidone or preparations containing 50 per cent or less of a mixture of any two or more of *N*-(*N*-dodecyl)-2-pyrrolidone, ***N*-methyl-2-pyrrolidone** or *N*-(*N*-octyl)-2-pyrrolidone **except** in preparations containing 25 per cent or less of designated solvents.

## Index

### *N*-(*N*-DODECYL)-2-PYRROLIDONE

cross reference: DESIGNATED SOLVENT, *N*-(*N*-OCTYL)-2-PYRROLIDONE, ***N*-METHYL-2-PYRROLIDONE**

*N*-methyl-2-pyrrolidone is also cross referenced in the Schedule 5 and index entries for *N*-(*N*-octyl)-2-pyrrolidone, as highlighted in the **red text** below:

## Schedule 5

*N*-(*N*-OCTYL)-2-PYRROLIDONE in preparations containing 50 per cent or less of:

- a) *N*-(*N*-octyl)-2-pyrrolidone or preparations containing 50 per cent or less of a mixture of any two or more of *N*-(*N*-octyl)-2-pyrrolidone, *N*-methyl-2-pyrrolidone or
- b) *N*-(*N*-dodecyl)-2-pyrrolidone except in preparations containing 25 per cent or less of designated solvents.

## Index

### ***N*-(*N*-OCTYL)-2-PYRROLIDONE**

cross reference: DESIGNATED SOLVENT, *N*-(*N*-DODECYL)-2-PYRROLIDONE, *N*-METHYL-2-PYRROLIDONE

### *Australian regulations*

- According to the [TGA Ingredient Database](#)<sup>262</sup> NMP is:
  - Available for use as an active ingredient in: biologicals, prescription medicines;
  - Available for use as an excipient ingredient in: biologicals, export only, prescription medicines; and
  - Not available as an equivalent ingredient in any application.
- As of 12 December 2019 there are 12 products currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#)<sup>263</sup> that contain NMP. Of these 12 products:
  - two products contain 160 mg NMP;
  - one product contains 165 mg NMP;
  - three products contain 193.9 mg NMP;
  - one product contains 258.5 mg NMP;
  - one product contains 278 mg NMP;
  - one product contains 833 mg NMP; and
  - for the remaining three, the NMP concentration has not been provided.
- The [Therapeutic Goods \(Permissible Ingredients\) Determination No. 4 of 2019](#)<sup>264</sup> does not include NMP as an ingredient permitted to be included in listed medicines.
- No results were found on the [Prescribing medicines in pregnancy database](#)<sup>265</sup> for NMP.
- There are no warning statements pertaining to NMP in the [Medicines Advisory Statement Specification 2019 \(RASML No.5 – Schedule 1\)](#).<sup>266</sup>
- According to the [Database of Adverse Event Notifications \(DAEN\)](#),<sup>267</sup> there are no reports of adverse events or deaths for products containing NMP as an active ingredient.
- As of 12 December 2019 there are 270 products (pesticides and veterinary parasiticides) containing NMP as a solvent currently approved for use by APVMA on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#).<sup>268</sup>

<sup>262</sup> <https://www.ebs.tga.gov.au/>

<sup>263</sup> <https://www.tga.gov.au/artg>

<sup>264</sup> <https://www.legislation.gov.au/Details/F2019L01597>

<sup>265</sup> <https://www.tga.gov.au/prescribing-medicines-pregnancy-database>

<sup>266</sup> <https://www.legislation.gov.au/Details/F2019L00213>

<sup>267</sup> <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

<sup>268</sup> <https://portal.apvma.gov.au/pubcris>



- APVMA's [Adverse Experience Reporting Program](#)<sup>269</sup> (AERP) reporting for NMP for the last 10 years included:
  - 2015: 1 total report and 1 total possible. Presenting signs (probable and possible): headache (1), malaise (1) and nausea (1);
  - 2014: 1 total report and 1 total possible. Presenting signs (probable and possible): lack of effect (1)

#### *International regulations*

- European Union cosmetics legislation contains provisions on the use of substances classified as carcinogenic, mutagenic, or toxic for reproduction (referred to as CMR substances) in cosmetic products. In general, the use of CMR substances is prohibited, apart from in exceptional cases. The [European Commission Cosmetic Ingredient Database](#)<sup>270</sup> lists NMP as a CMR substances of category 1A, 1B or 2. Therefore NMP is banned for use in cosmetic products.
- The [European Chemicals Agency \(ECHA\)](#)<sup>271</sup> hazard classification for NMP is, 'Danger!'. According to the harmonised classification and labelling (ATP09) approved by the European Union, NMP may damage the unborn child, causes serious eye irritation, causes skin irritation and may cause respiratory irritation. Additionally, the classification provided by companies to ECHA in [REACH](#)<sup>272</sup> registrations identifies NMP may damage fertility or the unborn child.
- NMP is listed in [REACH Annex XVII](#)<sup>273</sup> which restricts the use of NMP in consumer applications to <0.3 %. This effectively bans the use of NMP in consumer products as it would have no functionality at this level in present consumer applications.

#### ***Delegate's referral to ACCS #24***

***Pursuant to regulation 42ZCZK, the Delegate referred [proposed amendments to the Poisons Standard with respect to NMP, to the March 2019 meeting of the ACCS. No submissions were received in response to the notice inviting comment on the scheduling proposal.](#)***

#### ***Advice of ACCS #24***

In March 2019, the Advisory Committee on Chemicals Scheduling #24 (ACCS #24) considered an application to amend the Poisons Standard entry for *N*-methyl-2-pyrrolidone (NMP) in Schedule 6 to expand its use in cosmetics with a separate exemption concentration cut-off and to clarify the concentration cut-off for non-cosmetic use.

The Committee did not make a recommendation regarding the Applicant's proposal to amend the Poisons Standard with respect to *N*-methyl-2-pyrrolidone. This was largely because, the Committee did not reach a consensus on whether statements in the application relating to developmental toxicity were supported by the evidence presented. There were some reservations about the interpretation of the reproductive toxicity data, and the Committee was unable to provide advice to the Delegate until the reproductive toxicity data were clarified; specifically, it is unclear whether developmental toxicity outcomes were directly associated with the substance or were secondary to maternal toxicity. The status of the scheduling of products other than cosmetic could be affected depending on the outcome of the reproductive and developmental toxicity data assessment. The scheduling of designated solvents and other consumer products could also be affected. The Committee recommended that further toxicological evaluation of the reproductive toxicity data be sought.

As the Committee was unable to reach a consensus on whether statements in the application relating to developmental toxicity were supported by the evidence presented, consideration was not given to the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* at the meeting.

<sup>269</sup> <https://apvma.gov.au/node/10946>

<sup>270</sup> <https://ec.europa.eu/docsroom/documents/11382/attachments/1/translations>

<sup>271</sup> <https://echa.europa.eu/substance-information/-/substanceinfo/100.001.768>

<sup>272</sup> <https://echa.europa.eu/substances-restricted-under-reach/-/dislist/details/0b0236e1827f617f>

<sup>273</sup> <https://echa.europa.eu/substances-restricted-under-reach/-/dislist/details/0b0236e1827f617f>

### ***First interim decision***

On [6 June 2019](#),<sup>274</sup> the Delegate, under regulation 42ZCZN, at that time made an interim decision not to amend the Poisons Standard in relation to NMP and to seek further advice at the Joint Advisory Committee on Medicines and Chemicals Scheduling (Joint ACMS-ACCS) and further evidence on the reproductive toxicity data from the Applicant.

### ***First interim decision public submissions***

No public submissions were received in response to the notice published under regulation 42ZCZP advising of [the interim decision and invitation for further comment on substances referred to the March 2019 ACMS/ACCS meeting](#).<sup>275</sup>

### ***Summary of pre-meeting public submissions for ACCS-ACMS #23***

The Delegate did not engage in further public consultation when referring NMP to the November 2019 meeting of the Joint Committee on Medicines and Chemicals Scheduling (ACMS-ACCS #23).

### ***Summary of Joint ACMS-ACCS #23 advice/recommendations to the Delegate***

The Committee, while acknowledging the potential risks of any use of NMP, recommended that the TGA review the toxicology (especially the developmental toxicity) and safety of NMP use across all regulatory jurisdictions to provide more evidence to inform the need for further scheduling considerations.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) the risks and benefits of the use of a substance; (b) the purpose 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 that the Secretary considers necessary to protect public health.

The reasons for the advice included:

52E(1) Considerations	Reasons
a – the risks and benefits of the use of a substance	<i>Risks:</i> <ul style="list-style-type: none"><li>There is some evidence that NMP may be a developmental toxicant, especially if multiple products are used.</li></ul>
b – the purposes for which a substance is to be used and the extent of use of a substance	<ul style="list-style-type: none"><li>NMP has broad usage including as an ingredient in 12 prescription medicines, in 254 Agvet products, as a solvent in paint stripping, in automotive products, paints, varnishes, stain removers, writing inks and in some cosmetics.</li><li>Some use in cosmetics – mascara, skin moisturiser, hair dye stain remover.</li></ul>
c – the toxicity of a substance	<ul style="list-style-type: none"><li>There is some evidence that NMP may be a developmental toxicant. However, there is little human evidence and NMP has been used extensively for many years, including as an ingredient in prescription medicines.</li></ul>
d – the dosage, formulation, labelling, packaging and presentation of a substance	<ul style="list-style-type: none"><li>There are various presentations of NMP and a range of exposure routes.</li></ul>

<sup>274</sup> <https://www.tga.gov.au/book-page/22-interim-decision-relation-n-methyl-2-pyrrolidone>

<sup>275</sup> <https://www.tga.gov.au/scheduling-decision-interim/interim-decisions-and-invitation-further-comment-substances-referred-march-2019-acmsaccs-meetings>

e – the potential for abuse of a substance	<ul style="list-style-type: none"> <li>· Nil.</li> </ul>
f – any other matters that the Secretary considers necessary to protect public health	<ul style="list-style-type: none"> <li>· If NMP is considered to lead to a risk on the basis of developmental toxicity evidence, then a broad risk assessment may be necessary taking into account uses across different regulatory jurisdictions. The assessment of reproduction toxicity should include all available studies XXXXXXXXXXXXXXXXXXXXXXXX.</li> </ul>

### *Delegate's considerations*

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to NMP;
- The Meeting of the Advisory Committee on Chemicals Scheduling (ACCS #24)'s advice;
- The [Delegate's first interim decision](#);
- The Joint Meeting of the Advisory Committee on Chemicals Scheduling and the Advisory Committee on Medicines Scheduling (Joint ACMS-ACCS#23)'s advice;
- Section 52E of the *Therapeutic Goods Act 1989*, 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 that the Secretary considers necessary to protect public health;
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018);
- [Scheduling Handbook](#) (V 1.1, July 2019); and

### *Reasons for this interim decision*

I agree with the Committee's finding that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and 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 that the Secretary considers necessary to protect public health. packaging and presentation of a substance.

In my view, the relevant parts of the SPF 2018 are the Scheduling Factors for Schedule 6.

I have considered the available evidence in support of a Schedule 6 entry for NMP for cosmetics with a concentration cut-off of less than 2 per cent and a 25 per cent cut-off in other preparations involving non-cosmetic use and have made the decision that at this time, the current scheduling of NMP remains appropriate.

In March 2019, the ACCS #24 considered an application to amend the Schedule 6 entry for NMP to expand its use in cosmetics with a separate exemption concentration cut-off and to clarify the concentration cut-off for non-cosmetic use. The Committee were unable to reach a consensus on whether statements relating to developmental toxicity were supported by the evidence presented. Given the uncertainty regarding the likely exposure to NMP and the reliability of the summary of reproductive and developmental toxicity data, the Delegate at that time made an [interim decision](#)<sup>276</sup> not to amend the Poisons Standard in relation to NMP and to seek further evidence from the Applicant on matters listed in 52E(1) to clarify the reasons for their proposed amendment and to refer the matter to the Joint Advisory Committee on Medicines and Chemicals Scheduling given the number of medicines on the ARTG that contain NMP.

<sup>276</sup> <https://www.tga.gov.au/book-page/22-interim-decision-relation-n-methyl-2-pyrrolidone>

The main use of NMP that the Applicant raised in the original application as a concern was cosmetic use. However, the Applicant's proposed amendments did not align with international regulations and no evidence-based public-health rationale has been presented to support the proposed 2 per cent restriction. In the European Union, NMP is banned in cosmetics and for other consumer products, the concentration restriction will be lowered from 5% to 0.3% (GHS based – moving from specific concentration limit to generic concentration limit). This effectively will ban the use of NMP in all consumer products as it would have no functionality at this level in present consumer applications. Furthermore, a significant number of uses for NMP were identified outside of cosmetic use that were across a number of regulatory jurisdictions (i.e. TGA, APVMA and NICNAS) which needed to be taken into consideration if scheduling changes are to be implemented to protect public health. In addition to cosmetics, NMP was also used as an ingredient in human medicines, in agricultural and veterinary products, as a solvent in paints and paint strippers, in automotive products, varnishes and stain removers and in writing inks and it is unknown how many products are currently supplied in Australia. Given its broad usage and various presentations, NMP has a range of exposure routes for which there was currently insufficient evidence available to support that these uses pose unacceptable risks to the public. If changes to the scheduling of NMP were to be made on the basis of developmental toxicity, then a broad review of all its uses will be required to ensure that any scheduling changes address risks across all NMP uses, not only its cosmetic use.

While there is some evidence that NMP may be a developmental toxicant, there is little human evidence. Given the uncertainty regarding the interpretation of the reproductive toxicity data, it is unclear whether developmental toxicity outcomes are directly associated with NMP or are secondary to maternal toxicity. NMP has been used extensively for many years in a range of products, including as an ingredient in prescription medicines at up to 833 mg NMP per dose (subcutaneous injection with NMP comprising 50 per cent of the administered dose). While I note that products containing NMP currently on the ARTG are usually contraindicated in pregnancy due to the active ingredient, there has been no consideration given to the effects of these therapeutic concentrations of NMP on developmental outcomes. Furthermore, NMP is also present in high concentrations in paint strippers and automotive refinishing products; is a designated solvent at concentrations at up to 60 per cent in APVMA-approved agricultural and veterinary chemical products; and is present in many other industrial and domestic products. If the evidence on developmental toxicity is deemed significant enough to restrict concentration in cosmetics to 2 per cent, a careful consideration of all existing uses of NMP and its wide-spread use across all regulatory sectors is required to ensure any scheduling changes are based on all potential risks and not just risks associated with cosmetic use. In addition to the uncertainty regarding the developmental toxicity of NMP, there is also uncertainty regarding likely exposure to NMP given its use in a range of products that cross jurisdictional boundaries. This makes it difficult to ascertain the reasonable foreseeable harm to consumers and to assess the risk to human health from repeated use. Given these uncertainties, and the lack of safety signals warranting an amendment, the weight of evidence supports that on balance, the current scheduling of NMP remains appropriate.

I note that the US EPA has recently (November 2019) published a Draft Risk Evaluation for *N*-Methylpyrrolidone (NMP) and has sought public comment on its draft risk evaluation.<sup>277</sup> The finalised report (date to be determined by the authority) may provide information that reduces the uncertainty around the toxicity, and in particular the developmental toxicity, of NMP.

<sup>277</sup> <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/draft-risk-evaluation-n-methylpyrrolidone-nmp>