



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

10 June 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 March 2020;
- 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 **9 July 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 one of the email addresses provided below:

- [chemicals.scheduling@health.gov.au](mailto:chemicals.scheduling@health.gov.au) (for submissions relating to interim decisions made in relation to proposed amendments referred to the Advisory Committee on Chemicals Scheduling);  
or
- [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 subregulation 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 #29 March 2020)

## 1.1. Interim decision in relation to rizatriptan

### 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 down-schedule rizatriptan from Schedule 4 to Schedule 3 by amending the current Poisons Standard as follows:

#### Schedule 4 – Amend Entry

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

#### Schedule 3 – New Entry

RIZATRIPTAN when in divided oral preparations containing 5 milligrams or less per dosage unit and when sold in a pack containing not more than 2 dosage units for the acute relief of migraine in patients who have a stable, well-established pattern of migraine symptoms.

#### Appendix H – New Entry

RIZATRIPTAN

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

**1 February 2021**

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

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

- The [application](#) to amend the current Poisons Standard with respect to rizatriptan;
- Advisory Committee on Medicines Scheduling’s advice;
- The [public submissions](#) received in response to the [pre-meeting consultation](#);
- 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;
- [Scheduling handbook: Guidance for amending the Poisons Standard](#); and
- [Scheduling Policy Framework](#) (SPF 2018).

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

The Committee recommended down-scheduling of rizatriptan to Schedule 3 in the Poisons Standard as follows:

#### Schedule 4 – Amend Entry

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

### Schedule 3 – New Entry

RIZATRIPTAN when in divided oral preparations containing 5 milligrams or less per dosage unit and when sold in a pack containing not more than 2 dosage units for the acute relief of migraine in patients who have a stable, well-established pattern of migraine symptoms.

### Appendix H – New Entry

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In addition, the Committee recommended the Required Advisory Statements for Medicine Labels (RASML) statements align with the warning and advisory statements that are required and used in [New Zealand](#). These include:

- Chronic use can result in a rebound headache.
- Do not use if you have an irregular heartbeat.
- Do not use if you are allergic to sulfonamides.
- Do not use with other migraine medications except on doctor's advice.
- Do not use if you are pregnant except on doctor's advice.

The Committee did not recommend an implementation date to the delegate. The advice was for the TGA to consult with product sponsors on an appropriate implementation date taking into account the:

- timeframes required for packaging and labelling changes to be made; and
- proposed implementation dates for the related-triptans considered at the meeting of the ACMS in November 2019 (i.e. 1 February 2021), with a view to enacting the same date of effect for all three triptans.

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:

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

- Benefits
  - Rizatriptan provides effective treatment of acute migraine;
  - Well established safety profile when used as directed; and
  - Timely access for patients with confirmed migraine diagnosis may improve patient outcomes.
- Risks
  - Frequent use of rizatriptan may result in medication overuse headache;

- There are possible cerebral vascular side effects associated with rizatriptan as well as cardiovascular events;
  - Dizziness and somnolence were the most common drug related adverse effects;
  - Accidental and intentional overdose ;
  - Serotonin syndrome; and
  - Risk concerning potential delay in seeking medical advice.
- b) *the purposes for which a substance is to be used and the extent of use of a substance*
- Acute migraine that has been previously diagnosed by a medical practitioner.
- c) *the toxicity of a substance*
- Contraindications to use:
    - Uncontrolled hypertension;
    - Established coronary artery disease including ischaemic heart disease (IHD);
    - Signs and symptoms of IHD or Prinzmetal's angina;
    - History of stroke or transient ischaemic attack;
    - Peripheral vascular disease;
    - Cerebral vascular disease;
    - Basilar or hemiplegic migraine or 'atypical' headache;
    - Using another triptan; and
    - Used an ergotamine type medication within 6 hours.
  - Drug interactions can occur between triptans and selective serotonin reuptake inhibitors (SSRI/ Monoamine oxidase inhibitors (MAOIs). This can lead to serotonin syndrome however the likelihood serotonin syndrome of low.
  - Adverse effects are typically mild in intensity and transient.
  - Most common adverse effects dizziness, somnolence, and asthenia/ fatigue.
  - No toxic dose has been established.
- d) *the dosage, formulation, labelling, packaging and presentation of a substance*
- The recommended dose of rizatriptan is 10mg.
  - Doses should be separated by at least 2 hours, and no more than 30mg in any 24-hour period.
  - Formulations comes as tablets (orally disintegrating) or wafers:
    - Proposed pack size appropriate for intended use
    - Individual dose strength of 5mg of max. 10mg per pack appropriate dose for treatment of acute migraine attack
- e) *the potential for abuse of a substance*
- Overuse of triptans may be associated with medication overuse headache.
- f) *any other matters that the Secretary considers necessary to protect public health*
- Risk reduction can be further mitigated by pharmacist counselling and verification of diagnosis by a medical practitioner, if required.

### *Reasons for interim decision*

I have made an interim decision to down-schedule rizatriptan to Schedule 3 of the Poison Standard with restrictions on the dosage and indication. The reasons for my decision are set out below.

In making this decision, I considered that rizatriptan is most effective when taken as soon as possible following the onset of a migraine. It is my view that timely access to rizatriptan is a critical factor to improving patient outcomes. Removing the requirement for, patients with a confirmed diagnosis of migraine, to obtain a prescription from a GP will promote prompt access rizatriptan.

I have determined that rizatriptan meets the Schedule 3 Scheduling Factors in the Scheduling Policy Framework (SPF) 2018. I took into account that there is the potential for harm and adverse effects if rizatriptan is used inappropriately. The use of rizatriptan at established therapeutic dosage levels may mask the symptoms or delay diagnosis of more serious conditions. I understand there is the potential for drug interactions between rizatriptan and other drugs. All these factors are consistent with a Schedule 3 classification.

I am not persuaded that consumers are able to safely self-manage the symptoms of migraine without pharmacist input. I find that pharmacist intervention is necessary as the clinical response to triptan medicines can vary. Pharmacist will exercise professional judgment on the migraine pattern of the presenting patient and if necessary, refer the patient for verification of diagnosis by a medical practitioner. On balance, I consider the risk profile of rizatriptan is well defined and the adverse effects, interactions and contraindications are known, identifiable and manageable by a pharmacist.

I have made a decision restrict Schedule 3 rizatriptan for migraine because this medicine is not effective for other types of headache.

The SPF 2018 provides that the 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 rizatriptan directly to consumers and I have decided that it should be included in Appendix H.

I have made a decision not to include rizatriptan in Appendix M. I am satisfied that rizatriptan meets the Scheduling Factors under a Schedule 3 classification and that additional controls through inclusion in Appendix M are not necessary.

I have not made a decision on the RASML statements, as they are not relevant to the matters, which I must consider under section 52E of the *Therapeutic Goods Act 1989*. Accordingly, I have not given any weight to the ACMS recommendations insofar as it relates to the RASML statement and they were not material to my 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.

### *Implementation date*

I have decided on a **1 February 2021** implementation date to make rizatriptan available at the same time as sumatriptan, zolmitriptan, which were considered at the [November 2019 ACMS meeting](#). In making this decision, I considered that the availability of a range of triptans in Schedule 3 is in the interest of promoting public health as not all patients will respond to any given triptan.

## 1.2. Interim decision in relation to ondansetron

### 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 ondansetron. Specifically, not to down-schedule ondansetron from Schedule 4 to Schedule 3 as proposed by the applicant.

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

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

- The [application](#) to amend the current Poisons Standard with respect to ondansetron;
- Advisory Committee on Medicines Scheduling's advice;
- The [public submissions](#) received in response to the [pre-meeting consultation](#);
- 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;
- [Scheduling handbook: Guidance for amending the Poisons Standard](#); and
- [Scheduling Policy Framework](#) (SPF 2018).

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

The Committee recommended that the current scheduling of ondansetron remains appropriate.

Members agreed that the relevant matters under 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 reasons for the advice included:

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

- The application proposed that ondansetron be down scheduled to enable provision of this product by a pharmacist to a person presenting with nausea and/or vomiting of any cause.
- The application identified that the product was being widely used for indications outside of those approved by the TGA. The risks and benefits have not been assessed for any indications outside of those approved by the TGA and therefore the safety profile for use of this product for these conditions is not established.
- Limited evidence presented for indications outside those already approved that require medical diagnosis.

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

- Ondansetron is currently approved for the prevention of nausea and vomiting induced by cytotoxic therapy and radiotherapy and for the prevention of post-operative nausea and vomiting.
- Outside of treating nausea and vomiting associated with chemotherapy and radiotherapy or following a surgical procedure, the use and safety of ondansetron has not been assessed.

c) *the toxicity of a substance*

- The medication has potential to cause QTc interval prolongation in susceptible people, those with previous history, bradycardia, electrolyte imbalance, cardiac failure and those taking concomitant medicines which may cause QTc interval prolongation or electrolyte imbalance
- Patients may complain of headaches and constipation.
- Safety of ondansetron for use in human pregnancy has not been established as per TGA approved product information and as per therapeutic guidelines.

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

- Ondansetron is currently available as a tablet blister pack and solution for injection.

e) *the potential for abuse of a substance*

- NIL

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

- When a product is used off-label the medical practitioner takes full medico-legal responsibility for any adverse outcomes that result from prescribing off-label to a patient.

*Reasons for interim decision*

I have made an interim decision not to amend the current Poisons Standard in relation ondansetron. My view is that the current scheduling of ondansetron is appropriate. The detailed reasons for my decision follow.

Ondansetron is currently approved for the prevention of nausea and vomiting induced by cytotoxic therapy and radiotherapy; and for the prevention of post-operative nausea and vomiting. In my reading, the evidence establishes that both of these indications require management by a medical practitioner. Having considered the Scheduling Policy Framework 2018 (SPF 2018), I find that the requirement for medical practitioner intervention is consistent with the Scheduling Factors under a Schedule 4 classification.

I have considered the views expressed in the public submissions and those of the applicant, suggesting that that down-scheduling ondansetron to Schedule 3 would enable pharmacists to supply ondansetron for off-label use as is currently being practiced by medical practitioners. In my opinion, the distinguishing feature between pharmacist and medical practitioners initiating off-label supply is the degree of patient follow-up. The risks associated with off-label prescribing of ondansetron by medical practitioners are managed with appropriate diagnosis, management or monitoring and patient follow-up. I am concerned that these protections, in particular the provision of patient follow-up, would not be adequately in place under the care of a pharmacist.

I have considered the [safety alert](#) on published by the Therapeutic Goods Administration (TGA) in 2012 regarding the use of ondansetron and the associated risk of QTc interval prolongation, which I find are relevant to my decision. It is my view that close monitoring by a medical practitioner is necessary in patients who have or may develop QTc interval prolongation, including those with electrolyte abnormalities, congestive cardiac failure, bradycardias or who take medicines.

The applicant has not presented, and I have not found, any compelling evidence that establishes pharmacist can supply odansetron to consumers outside the current approved indications with reasonable safety. In particular, I note with concern that the safety and effectiveness of ondansetron for the treatment of conditions outside of the approved indications have not been assessed by the TGA.

Having considered the need for medical practitioner oversight for the current approved indications and the risks to consumers associated with off-label in a pharmacy setting I am of the firm view that the current scheduling of odansetron is appropriate.

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; and (f) any other matters that the Secretary considers necessary to protect public health.

## 1.3. Interim decision in relation to melatonin

### 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 down-schedule melatonin in modified release formulations from Schedule 4 to Schedule 3 by amending the current Poisons Standard as follows:

#### Schedule 4 – Amend Entry

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

#### Schedule 3 – New Entry

**MELATONIN in modified release tablets containing up to 2 mg of melatonin for the treatment of primary insomnia for adults aged 55 or over, in packs containing not more than 30 tablets.**

#### APPENDIX H – New Entry

**MELATONIN**

#### Index – Amend Entry

**MELATONIN**

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

**1 October 2020**

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

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

- The [application](#) to amend the current Poisons Standard with respect to melatonin;
- Advisory Committee on Medicines Scheduling’s advice;
- The [public submissions](#) received in response to the [pre-meeting consultation](#);
- Section 52E of the *Therapeutic Goods Act 1989*, in particular (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 (e) the potential for abuse of a substance;
- [Scheduling handbook: Guidance for amending the Poisons Standard](#); and
- [Scheduling Policy Framework](#) (SPF 2018).

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

The Committee recommended the down-scheduling of melatonin to Schedule 3 in the Poisons Standard as follows:

#### Schedule 4 – Amend Entry

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

#### Schedule 3 – New Entry

**MELATONIN in modified release tablets containing up to 2 mg of melatonin for the treatment of primary insomnia for adults aged 55 or over, in packs containing not more than 30 tablets.**

## APPENDIX H – New Entry

### MELATONIN

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The Committee recommended the following Required Advisory Statements for Medicine Labels (RASML) statement to the Over the Counter Evaluations Section at the Over-the-Counter Medicines Evaluation Section at the TGA:

1. Do not use this product if you have impaired liver function or autoimmune disease or taking other medications. Consult your doctor or pharmacist.
2. Do not use if you are pregnant or breastfeeding. Consult your doctor.
3. Do not use in children and adolescent under 18 years of age.
4. Do not use if you are allergic to melatonin. If you get an allergic reaction, stop taking and seek medical advice immediately.
5. Consumption with alcohol, other medications or natural health products with sedative properties is not recommended.
6. This product may cause drowsiness

The Committee also recommended an implementation date of **1 October 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 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 (e) the potential for abuse of a substance.

The reasons for the advice included:

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

- Benefits:
  - Well tolerated and offers a safer alternative to benzodiazepines, sedating anti-depressants and over the counter sedating antihistamines to treat insomnia patients over 55 years of age.
- Risks:
  - Hypersensitivity reactions, hepatic impairment, autoimmune diseases, drug interactions e.g. fluvoxamine, cigarette smoking, hypnotics, alcohol, pregnancy, use in lactation.
  - The risks associated with melatonin can be adequately managed including during patient-pharmacist counselling and use of Cautionary Advisory Labels.

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

- The TGA-approved indication is for ‘Monotherapy for the short term treatment of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over.’

c) *the toxicity of a substance*

- Mild side effects have been reported with higher doses including drowsiness, daytime sleepiness, headaches and nausea.

- No evidence suggests that people develop tolerance to melatonin or dependency or withdrawal effects or rebound insomnia
  - Established safety profile when used for up to 6 months and there is some evidence that melatonin can be used safely for up to 2 years in some patients.
  - TGA approved Product Information indicates administration of daily doses of up to 300 mg of melatonin without causing clinically significant adverse reactions have been reported in the literature. If overdose occurs, drowsiness is to be expected.
- d) *the dosage, formulation, labelling, packaging and presentation of a substance*
- The dosage of the slow release formulation is 2 mg once daily 1-2 hours before bedtime and after food. This dosage may be continued for up to thirteen weeks.
- e) *the potential for abuse of a substance*
- The potential for abuse of this medication is limited. It is not a drug of addiction and it has no euphoric effect.
  - It cannot be converted into another more active substance for illicit use.

#### *Reasons for interim decision*

I have made an interim decision to down-schedule melatonin in modified release formulations to Schedule 3 of the Poison Standard with restrictions on age and pack size. The reasons for my decision are set out below.

Melatonin is currently approved for monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over. In my opinion, the risk profile of melatonin is well defined and the adverse effects, interactions and contraindications are known, identifiable and manageable by a pharmacist. I have not identified any compelling evidence, which establishes that melatonin can be safely supplied to consumers, by a pharmacist, outside the current approved indications.

I am satisfied that melatonin, when supplied in accordance with the current approved indications, meets the Scheduling Factors for Schedule 3. Insomnia does not require medical diagnosis or only requires initial medical diagnosis, and the consumer does not require close medical management. I find that consumer consultation with a pharmacist is necessary to reinforce and/or expand on aspects of the safe use and appropriate supply in line with the approved indications. The use of melatonin is not expected to produce dependency at either the established therapeutic dose or at supra-therapeutic doses. There may be potential for harm if melatonin is used inappropriately, however, I am satisfied that it is substantially safe with pharmacist intervention. Where risk of misuse, abuse or illicit use is identified, again, I am satisfied that the risk can be minimised through pharmacist-consumer consultation.

I have made a decision not to include melatonin in Appendix M. I am satisfied that melatonin meets the Scheduling Factors under a Schedule 3 classification and that additional controls through inclusion in Appendix M are not necessary.

Having considered the matters set out in the Guidelines for advertisements for medicines containing Schedule 3 substances, I have deliberated on the potential sedating effects of melatonin and its suitability for inclusion in Appendix H. I am satisfied that daytime sedation effects are small and in comparison to other Schedule 3 sedatives, the potential for melatonin-induced sedation is milder and less common. It is my understanding that melatonin has a very short half-life of 20 to 50 minutes. The evidence demonstrates that the sedative effects of melatonin are not likely to impact on safety to drive or cognition more generally while under the effect of melatonin or the following day.

It is my view that melatonin has a better safety profile than the existing over the counter options for insomnia, especially in older people i.e. the 55 years and over age group, who are more sensitive to the anticholinergic side effects of sedating antihistamines. For many older patients, melatonin

would represent a better option in preference to long-term use of benzodiazepines or the non-benzodiazepines used for insomnia. I have considered that there may be public health benefit in increasing awareness of the Schedule 3 availability of melatonin for use within the permitted indication. On the balance of evidence, I find that melatonin is appropriate for inclusion in Appendix H to allow it to be advertised for the approved indication.

I have not made a decision on the RASML statements, as they are not relevant to the matters, which I must consider under section 52E of the *Therapeutic Goods Act 1989*. Accordingly, I have not given any weight to the ACMS recommendation insofar as it relates to the RASML statements and they were not material to my 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; and (e) the potential for abuse of a substance.

*Implementation date*

I have decided the appropriate implementation date is **1 October 2020**.

## 1.4. Interim decision in relation to adapalene

### 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 down-schedule adapalene in topical preparations by amending the current Poisons Standard as follows:

#### Schedule 4 – Amend Entry

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

#### Schedule 3 – New Entry

ADAPALENE in topical preparations containing 0.1 per cent or less of adapalene for the treatment of *acne vulgaris* in adults and in children over 12 years of age.

#### Appendix H – New Entry

ADAPALENE

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ADAPALENE

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

**1 June 2021**

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

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

- The [application](#) to amend the current Poisons Standard with respect to adapalene;
- Advisory Committee on Medicines Scheduling’s advice;
- The [public submissions](#) received in response to the [pre-meeting consultation](#);
- Section 52E of the *Therapeutic Goods Act 1989*, in particular (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 (e) the potential for abuse of a substance;
- [Scheduling handbook: Guidance for amending the Poisons Standard](#); and
- [Scheduling Policy Framework](#) (SPF 2018).

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

The Committee recommended the down-scheduling of adapalene to Schedule 3 in the Poisons Standard as follows:

#### Schedule 4 – Amend Entry

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

#### Schedule 3 – New Entry

ADAPALENE in topical preparations containing 0.1 per cent or less of adapalene for the treatment of *acne vulgaris* in adults and in children over 12 years of age.

## Appendix H – New Entry

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### ADAPALENE

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The Committee recommended that the TGA amend the Required Advisory Statements for Medicine Labels (RASML) statement to align with the Consumer Medicines Information Leaflet.

The Committee also recommended an implementation date of **1 June 2021**.

The reasons for the advice included:

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

- Risks:
  - Adapalene is associated with localised skin reactions.
  - Main risk is associated with use in pregnancy and breastfeeding as adapalene is potential teratogenicity.
  - Skin irritation and photosensitivity are common adverse events especially in the first weeks of treatment;
  - No photocarcinogenicity studies have been conducted, however there are concerns based on animal laboratory studies of other retinoids that exposure to UV sunlight may be associated with increased risk; and
- Benefits:
  - Effective topical treatment for *acne vulgaris*.

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

- Mild acne.
- Used for *acne vulgaris* – treatment of comedo, popular and pustular acne on the face, chest or back.
- Extent of use – very widely used especially in adolescents; long history of use (more than 20 years – first registered November 1995).

c) *the toxicity of a substance*

- Low systemic toxicity when used topically.
- Retinoids as a class are known to be teratogenic, although no teratogenic effects were seen in animals when administered orally at up to 120x the maximum daily human topical dose.
- Cutaneous use up to 150 x maximum daily human topical dose showed no teratogenic effects therefore indicating a margin of safety.

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

- Concentration cut-off of 0.1% will prompt medical referral to patients unresponsive to single ingredient or low strength combination adapalene products.
- Proposed labelling was not provided by applicant however warning statements regarding pregnancy, breastfeeding, skin irritation, use of sunscreen and expectations of therapy are appropriate.

e) *the potential for abuse of a substance*

- Adapalene may be used off-label for cosmetic (anti-aging) purposes, however the Schedule 3 classification will be restricted to human therapeutic use thereby prohibiting the over-the-counter supply by pharmacists for this purpose.

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

- NIL



### *Reasons for interim decision*

I have made an interim decision to down-schedule adapalene to Schedule 3 of the Poison Standard with restrictions on the preparation and indication. The reasons for my decision are set out below.

Adapalene is a topical retinoid indicated for comedo, papular or pustular acne of the face, chest and back. It is a potent modulator of cellular differentiation, keratinisation and inflammatory processes, all of which are features in the pathology of *acne vulgaris*. I made a decision to restrict the indication to *acne vulgaris* to capture the current approved indication.

Based on my reading of the available data, the most significant area of concern is teratogenicity associated with adapalene use during pregnancy. Adapalene is classified as a Category D medicine, which means it is in a class of medicines, which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. I have taken into account that the evidence demonstrates that cutaneous use up to 150 times the maximum daily human topical dose showed no teratogenic effects indicating there is a margin of safety. I recognise that there may be individual factors such as damaged skin barrier or excessive use that could contribute to increased systemic exposure. I am satisfied that pharmacists are suitably qualified to be able to assess and counsel patients to ensure the quality use of adapalene under a Schedule 3 classification. I am additionally reassured that product labelling, implemented through other legislation, is a mitigating factor to protect against the risks to pregnancy. On the balance of evidence, I am satisfied that adapalene, when supplied in a topical preparation is associated with very low systemic exposure and is substantially safe with pharmacist intervention to ensure its quality use.

My decision to include an age restriction in the Schedule 3 entry for adapalene was made on the basis that the safety and efficacy of adapalene use in children below 12 years has not been established.

I agree with the proposed 0.1% concentration cut-off as proposed by applicant. I consider 0.1% to be a relatively low cut off in the context of products currently available on the market. Consumer consultation with a pharmacist is necessary to reinforce and/or expand on aspects of the safe use of adapalene at the proposed concentration. I am satisfied that, with pharmacist intervention, supply single ingredient preparations, and the low strength combination preparation can be supplied without medical practitioner intervention.

I have made a decision not to support the applicant's proposal to include cosmetic use in the Schedule 3 entry because the safety and efficacy of adapalene for cosmetic use has not been demonstrated. I have had particular regard for the public submission from the College of Dermatologists who were firmly opposed to the inclusion of cosmetic use. I understand that pharmacists are not trained to consult on cosmetic medicine. I am concerned that the off-label supply of adapalene by a pharmacist for cosmetics purposes may result in poor management and an increase in adverse events. I find that the inclusion of cosmetic use in the Schedule 3 entry to be problematic as it is more likely to exacerbate off-label use for cosmetic purposes rather than for medicinal treatment of acne. It may imply that the product can be used for photo-aging, blemishes or other off label uses.

I have deliberated on the appropriateness of adapalene for advertising given its teratogenic properties. Having considered the matters set out in the Guidelines for advertisements for medicines containing Schedule 3 substances I am satisfied that the risks of teratogenicity are low in topical preparations and that any risk can be controlled through pharmacist counselling and product labelling. It is my opinion that the risks associated with teratogenicity will not be exacerbated by advertising.

I have made a decision not to include adapalene in Appendix M. I am satisfied that adapalene meets the Scheduling Factors under a Schedule 3 classification and that additional controls through inclusion in Appendix M are not necessary.

I have not made a decision on the RASML statements, as they are not relevant to the matters, which I must consider under section 52E of the *Therapeutic Goods Act 1989*. Accordingly, I have not given

any weight to the ACMS advice insofar as it relates to the RASML statements and they were not material to my 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.

*Implementation date*

I have decided the appropriate implementation date is **1 June 2021** to allow a transition time for labelling changes to be made.

## 1.5. Interim decision in relation to Selective Serotonin Reuptake Inhibitors (SSRI)

### 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 include a Selective Serotonin Reuptake Inhibitors (SSRI) group entry.

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

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

- The [scheduling proposal](#) to amend the current Poisons Standard with respect to a Selective Serotonin Reuptake Inhibitors (SSRI) group entry;
- Advisory Committee on Medicines Scheduling's advice;
- The [public submissions](#) received in response to the [pre-meeting consultation](#);
- Section 52E of the *Therapeutic Goods Act 1989*, in particular (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;
- [Scheduling handbook: Guidance for amending the Poisons Standard](#); and
- [Scheduling Policy Framework](#) (SPF 2018).

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

The Committee did not recommend a SSRI class entry.

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:

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

- Risks:
  - SSRIs exert secondary physiological effects on the body due to their effects on various neurotransmitter receptors, and depending on the individual agent, slightly different adverse event profiles are produced.
  - Some adverse effects are serious and severe, and some are frequent. These may include sexual dysfunction, suicide risk, decreased appetite, dry mouth, headache, nausea, agitation, cardiac disturbances.
  - SSRIs can interact with other drugs and reduce their efficacy, cause adverse effects, or cause dangerous reactions such as serotonin syndrome.
  - Abrupt cessation of SSRI medicines can cause a withdrawal syndrome.
- Benefits:
  - Effective treatment for depressive disorders with a better safety profile compared to many other treatments.
  - SSRI medicines can effectively treat serious mental health conditions.

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

- SSRI medicines are used to treat health conditions such as depression, anxiety and eating disorders, the safe treatment of which requires the supervision of a medical practitioner, which is achieved by including SSRI medicines in Schedule 4.
- Due to their relative safety compared to other antidepressants, SSRIs are commonly used.

c) *the toxicity of a substance*

- Medical intervention needed due to drug interactions and increased risk of adverse effects, including serotonin syndrome.
- Abrupt cessation of treatment with SSRIs can lead to withdrawal / discontinuation syndrome.
- In overdose, SSRI are rarely fatal. The risk of toxicity and death is higher if taken with other drugs or alcohol.

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

- Many products registered on the ARTG – all are Schedule 4.

e) *the potential for abuse of a substance*

- SSRIs are not demonstrated to have a dependence liability.

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

- A class SSRI entry may not capture intended substance and/ or may create ambiguity in the scheduling.

*Reasons for interim decision*

I have made an interim decision not to amend the current Poisons Standard in relation to the proposal to include a Selective Serotonin Reuptake Inhibitors (SSRI) group entry. My detailed reasons follow.

It is my view that as a legislative instrument it is important that the Poisons Standard is specific and unambiguous. I find it problematic that the group entry, as proposed, is ambiguous in its intended capture. I have considered a scenario where a substance that satisfies the risk profile for Schedule 4 may not be captured by the proposed group entry. I have also considered an alternative scenario whereby lower risk substances may be inadvertently captured by the group entry. In addition, the group entry, as proposed, is likely to create uncertainty with respect to herbal extracts with potentially SSRI-like action e.g. St John's Wort.

In making my decision, I considered whether there is an urgent public health concern that would warrant the need for an SSRI group entry. I have not identified compelling evidence that establishes the provision of an SSRI group entry is required to be in place to protect health.

I agree with the Committee's finding that the relevant provisions of 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.

## 1.6. Interim decision in relation to ranitidine

### Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment to increase the pack sizes available for general sale and in pharmacies for ranitidine, made an interim decision not to amend the current Poisons Standard.

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

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

- The [application](#) to amend the current Poisons Standard with respect to ranitidine;
- Advisory Committee on Medicines Scheduling's advice;
- The [public submissions](#) received in response to the [pre-meeting consultation](#);
- 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;
- [Scheduling handbook: Guidance for amending the Poisons Standard](#); and
- [Scheduling Policy Framework](#) (SPF 2018).

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

The Committee recommended that the scheduling of ranitidine in the Poisons Standard remains appropriate.

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; and (e) the potential for abuse of a substance.

The reasons for the advice included:

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

- Risks:
  - Masking symptoms of more serious underlying conditions such as gastric cancer, undiagnosed peptic ulcer or gastro-oesophageal reflux.
  - Increased availability in general sale and Schedule 2 may prolong potential treatment periods without advice from a healthcare professional.
- Benefits:
  - Effective relief of symptoms of gastro-oesophageal reflux; and
  - Ease of access and convenience with larger pack sizes.

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

- Relief of symptoms of gastro-oesophageal reflux.

#### *c) the toxicity of a substance*

- Risk profile is well defined.
- The potential for harm from inappropriate use is low.

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

- The proposed pack size is not consistent with short term treatment.

- Ranitidine is currently listed in Schedules 2 and 4, with an exemption to allow general sales of small quantities of both 150mg (7 dosage units) and 300 mg (14 dosage units) tablets.

e) *the potential for abuse of a substance*

- Low/minimal.
- Potential for long term inappropriate use with larger pack sizes.

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

- NIL.

*Reasons for interim decision*

I have made an interim decision not to amend the current Poisons Standard in relation ranitidine. My view is that the current scheduling of ranitidine is appropriate. The detailed reasons for my decision follow.

It is my view that pharmacist intervention, currently in place, is the critical mitigating factor to ensure the quality use of ranitidine. Increased pack sizes of ranitidine available at the general sales level and Schedule 2 would remove the opportunity for pharmacist interaction and increase the potential for harm to consumers.

I have identified a number of factors, which would necessitate consumer consultation with a pharmacist to reinforce and/or expand on aspects of the safe use of ranitidine. These include, the use of the ranitidine at established therapeutic dosage levels may mask the symptoms or delay diagnosis of a serious condition or lead to sub-optimal treatment of conditions such as Gastro-oesophageal reflux disease (GORD). Pharmacist intervention is required to detect the masking of a serious disease or compromising medical management of a disease, and to deal with it appropriately.

Based on my assessment, I find that the net benefit associated with access to ranitidine at the general sales level or Schedule 2 is limited to convenience for consumers. Whilst ranitidine has a favourable safety profile, there is no compelling evidence to suggest that current access is inadequate. In my view, the benefit of convenience does not sufficiently outweigh the risk of harm associated ranitidine use set out above.

I disagree with the views expressed by the applicant that, increasing the pack size in the Schedule 2 would ensure patients have continued access to counselling for the safe use of the product. In my opinion, a larger pack size may delay medical review for more severe gastro-oesophageal disease or complications. On balance, I find that an increase in the pack size availability is inconsistent with the quality use of ranitidine.

I agree with the Committee's finding that the relevant provisions of 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.

## 1.7. Interim decision in relation to fexofenadine

### Interim decision

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

#### Schedule 4 – Amend Entry

FEXOFENADINE **except**:

- a) when included in Schedule 2;
- b) ~~or in divided preparations~~ for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:
  - i) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and
  - ii) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine;
- c) for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:
  - i) in a primary pack containing 5 dosage units or less and not more than 5 days' supply; and
  - ii) labelled with a recommended daily dose not exceeding 180 mg of fexofenadine; or
- d) for the treatment of seasonal allergic rhinitis and children 6 years of age and over when:
  - i) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and
  - ii) labelled with a recommended daily dose not exceeding 60 mg of fexofenadine.

#### Schedule 2 – Amend Entry

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

- a) for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:
  - i) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and
  - ii) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine;
- b) for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:
  - i) in a primary pack containing 5 dosage units or less and not more than 5 days' supply; and
  - ii) labelled with a recommended daily dose not exceeding 180 mg of fexofenadine; or
- c) for the treatment of seasonal allergic rhinitis and children 6 years of age and over when:
  - i) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and
  - ii) labelled with a recommended daily dose not exceeding 60 mg of fexofenadine.

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

**1 October 2020**

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

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

- The [application](#) to amend the current Poisons Standard with respect to fexofenadine;
- Advisory Committee on Medicines Scheduling's advice;
- The [public submissions](#) received in response to the [pre-meeting consultation](#);
- Section 52E of the *Therapeutic Goods Act 1989*, in particular (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;
- [Scheduling handbook: Guidance for amending the Poisons Standard](#); and
- [Scheduling Policy Framework](#) (SPF 2018).

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

The Committee recommended that the scheduling of fexofenadine in Schedule 2 and Schedule 4 be amended in the Poisons Standard as follows:

#### **Schedule 4 – Amend Entry**

FEXOFENADINE **except**:

- a) when included in Schedule 2;
- b) ~~or in divided preparations~~ for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:
  - i) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and
  - ii) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine;
- c) for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:
  - i) in a primary pack containing 5 dosage units or less and not more than 5 days' supply; and
  - ii) labelled with a recommended daily dose not exceeding 180 mg of fexofenadine; or
- d) for the treatment of seasonal allergic rhinitis and children 6 years of age and over when:
  - i) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and
  - ii) labelled with a recommended daily dose not exceeding 60 mg of fexofenadine.

#### **Schedule 2 – Amend Entry**

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

- a) for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:
  - i) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and



- ii) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine;
- b) for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:
  - i) in a primary pack containing 5 dosage units or less and not more than 5 days' supply; and
  - ii) labelled with a recommended daily dose not exceeding 180 mg of fexofenadine; or
- c) for the treatment of seasonal allergic rhinitis and children 6 years of age and over when:
  - i) in a primary pack containing 20 dosage units or less and not more than 10 days' supply; and
  - ii) labelled with a recommended daily dose not exceeding 60 mg of fexofenadine.

The Committee also recommended an implementation date of **1 October 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:

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

- The benefits of broadening the availability of fexofenadine for general sale to 180mg tablets (5 days supply) for people aged over 12 years outweighs potential risks of improper use.

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

- Seasonal allergic rhinitis is a common, easily identified condition that is appropriate for self-management where non-treatment can affect a sufferer's quality of life.
- Second generation non-sedating anti-histamine approved for relief of seasonal allergic rhinitis.

c) *the toxicity of a substance*

- Established safety profile with low risk of sedation.
- No significant increase in risk with increased dose from 120mg/day to 180mg/day.
- The safety profile is well defined fexofenadine is substantially safe for use.
- Lack of sedative effect, low abuse potential, wide therapeutic index, well-established toxicity profile, not associated with significant ECG abnormalities.

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

- Tablets and liquids are available. Liquid formulations are intended for use in children under 6 and the scheduling of this formulation should remain unchanged.
- Recommend in divided preparations only.

e) *the potential for abuse of a substance*

- NIL

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

- NIL

### *Reasons for interim decision*

I have made an interim decision to amend the Schedule 2 and Schedule 4 entries for fexofenadine in the Poison Standard. The reasons for my decision are set out below.

It is my view that the net benefits of broadening the availability of fexofenadine to general sale in 180mg tablets (5 day supply) for people aged over 12 years outweighs the potential risks associated with improper use. In coming to this decision, I considered that fexofenadine has an established safety profile with no evidence of greater risk associated with increased dose from 120mg to 180mg. I am satisfied that the dose and safety of fexofenadine in children aged 6-12 for the treatment of seasonal allergic rhinitis is well established. I have considered that the evidence establishes that fexofenadine-containing products have limited propensity for overdose.

Based on my reading of the data I have identified that the main risk to public health associated with down-scheduling to the general sales level is the potential for dosing errors in liquid formulations intended for children less than 6 years of age. I have made a decision to restrict the dosage form to "divided preparations" to ensure that liquid formulations remain scheduled to mitigate the risk of misuse in children.

I am satisfied that fexofenadine can be supplied at the general sales level, with reasonable safety, without any access to health professional advice. It is my view that the criteria for 'reasonable safety' as set out in the Scheduling Handbook are satisfied. Taking the mitigating factors for liquid formulations into consideration, I find that fexofenadine can be supplied at the general sales level, with reasonable safety, without any access to health professional advice.

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.

### *Implementation date*

I have decided the appropriate implementation date is **1 October 2020**.

## 1.8. Interim decision in relation to flurbiprofen

### Interim decision

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

#### Schedule 4 – Amend Entry

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

#### Schedule 2 – Amend Entry

FLURBIPROFEN in preparations for topical oral use when:

- a) in divided preparations containing 10 mg or less of flurbiprofen per dosage **unit except when:**
  - i) **for the treatment of adults and children over 12 years of age; and**
  - ii) **in a primary pack containing not more than 16 dosage units.**
- b) in undivided preparations containing 0.25 percent or less or 10 mg or less per dose of flurbiprofen.

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##### FLURBIPROFEN

Schedule 4

Schedule 2

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

**1 October 2020**

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

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

- The [application](#) to amend the current Poisons Standard with respect to flurbiprofen;
- Advisory Committee on Medicines Scheduling's advice;
- The [public submissions](#) received in response to the [pre-meeting consultation](#);
- Section 52E of the *Therapeutic Goods Act 1989*, in particular (a) the risks and benefits of the use of a substance; (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;
- [Scheduling handbook: Guidance for amending the Poisons Standard](#); and
- [Scheduling Policy Framework](#) (SPF 2018).

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

The Committee recommended that amendments to the current Schedule 4 and Schedule 2 entries for flurbiprofen in the Poisons Standard as follows:

#### Schedule 4 – Amend Entry

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

## Schedule 2 – Amend Entry

FLURBIPROFEN in preparations for topical oral use when:

- a) in divided preparations containing 10 mg or less of flurbiprofen per dosage unit **except when:**
  - i) for the treatment of adults and children over 12 years of age; and
  - ii) in a primary pack containing not more than 16 dosage units.
- b) in undivided preparations containing 0.25 percent or less or 10 mg or less per dose of flurbiprofen.

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#### FLURBIPROFEN

Schedule 4

Schedule 2

The Committee also recommended an implementation date of **1 October 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 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.

The reasons for the advice included:

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

- The Schedule 2 exemption for flurbiprofen meets the Scheduling Handbook’s criteria for ‘reasonable safety’ criteria.
  - Benefits:
    - Equivalent or better risk/benefit profile than systemic oral analgesics/anti-inflammatories which may be used for the same purpose.
    - Clinically meaningful pain relief provided by flurbiprofen lozenges
    - Flurbiprofen demonstrated superiority over demulcent only lozenges (non-medicated) for self-medication of sore throat.
  - Risks:
    - Is classified a Category B2 medication for pregnancy.
    - Risk of idiosyncratic reaction is very rare.
    - Should not be used by children < 12 years.
    - Same risk profile as all NSAIDs (but systemic exposure much less):
      - Risk in those with asthma, allergies to NSAIDs or aspirin.
      - Risk in those with heart failure, kidney disease, liver disease, peptic ulcer.
      - Interaction with certain medications (anti-hypertensives, methotrexate, anticoagulants).
    - Risk of concomitant use of oral NSAIDs.
- b) *the purposes for which a substance is to be used and the extent of use of a substance*
- Indication is for the relief of pain, swelling and inflammation of a severe sore throat.

c) *the toxicity of a substance*

- The toxicity of flurbiprofen is considered very low: there is very low buccal systemic absorption, 10% of approved oral dose of same medication.

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

- Lozenge formulation.
- 8.75mg lozenges in a blister pack of 16.
- Risk warnings on the packaging.

e) *the potential for abuse of a substance*

- NIL

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

- NIL

*Reasons for interim decision*

I have made an interim decision to amend the Schedule 2 and Schedule 4 entries for flurbiprofen in the Poison Standard. The reasons for my decision are set out below.

In my opinion, the net benefits of broadening the availability of flurbiprofen to the general sale level with restrictions placed on age and dosage form combined with warning labels outweighs the potential risks associated with improper use.

In coming to this decision, I considered that flurbiprofen lozenges have the potential to improve the self-management of sore throats. I also took into account that pain relief associated with flurbiprofen use has been confirmed in a number of randomised controlled clinical trials in the literature, which demonstrate meaningful pain relief and better pain control than demulcents. I am satisfied that the risks associated with the potent Nonsteroidal anti-inflammatory drugs (NSAID) activity of flurbiprofen can be mitigated by its preparation as a lozenge, which has very low buccal systemic absorption. I accept the evidence that the low bioavailability of the lozenge preparation will minimise the known drug interactions and contraindications.

It is my view that the abuse potential of flurbiprofen lozenges is small based on my assessment of the accounts of misuse, intentional misuse and intentional overdose in the Worldwide Reckitt Benckiser Periodic Safety Update Report (PSUR) data and in the data presented in a public submission from the NSW Poisons Information Centre. On the balance of evidence, I am satisfied that there is a net benefit to public health in greater access to flurbiprofen at the general sales level.

I have decided to include a pack size limit of sixteen dosage units. My assessment is that this pack size limit amounts to two days' supply if the maximum of eight tablets per day is consumed. I understand this pack size to be in line with the Therapeutic Guidelines for Management of Acute Pharyngitis/Tonsillitis in Australia. I note that similar products available at the general sales levels currently have larger pack size limits in place e.g. unscheduled oral ibuprofen is available in twenty-four units (four days) and paracetamol in twenty units (two and a half days).

I made a decision to include specific warning label against the use of flurbiprofen in children less than twelve years of age to mitigate the risk of inappropriate use. My decision to include a mandatory warning label is consistent with the request from the public submissions from the NSW Poisons Information Centre and Australian Medical Association.

Taking into account the restrictions on age and dosage form described above, I am satisfied that flurbiprofen lozenges are able to be supplied at the general sales level, with reasonable safety, without any access to health professional advice. It is my view that the criteria for 'reasonable safety' as set out in the Scheduling Handbook are satisfied.

I have made a decision to not allow the supply of flurbiprofen throat sprays at the general sales level. I have not identified compelling data to establish this preparation could be supplied at the general sales level with reasonable safety.

I agree with the Committee's finding that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are 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; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

*Implementation date*

I have decided the appropriate implementation date is **1 October 2020**.

## 2 Interim decisions on proposed amendments referred to the Advisory Committee on Chemicals Scheduling (ACCS #27, March 2020)

### 2.1. Interim decision in relation to carbetamide

#### 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 carbetamide as follows:

#### Schedule 6 – New Entry

**CARBETAMIDE.**

#### Appendix B – Delete Entry

SUBSTANCE	DATE OF ENTRY	REASON FOR LISTING	AREA OF USE
CARBETAMIDE	Aug 1991	a	1
a = Low Toxicity 1 = Agriculture			

#### INDEX – Amend Entry

**CARBETAMIDE**

Appendix B, Part 3

**Schedule 6**

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

**1 October 2020**

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

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

- The [application](#) to amend the current Poisons Standard with respect to carbetamide;
- 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; and (c) the toxicity of a substance;
- [Scheduling handbook: Guidance for amending the Poisons Standard](#); and
- [Scheduling Policy Framework](#) (SPF 2018).

#### *Pre-meeting public submissions*

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

*Summary of ACCS advice/recommendations to the Delegate*

The Advisory Committee on Chemicals Scheduling recommended that the scheduling of carbetamide be rescheduled from Appendix B to Schedule 6 in the Poisons Standard as follows:

**Schedule 6 – New Entry**

**CARBETAMIDE.**

**Appendix B – Delete Entry**

SUBSTANCE	DATE OF ENTRY	REASON FOR LISTING	AREA OF USE
CARBETAMIDE	Aug 1991	a	1
a = Low Toxicity 1 = Agriculture			

**INDEX – Amend Entry**

**CARBETAMIDE**

~~Appendix B, Part 3~~

**Schedule 6**

The reasons for the advice included:

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

- Benefits
  - Herbicide used for human and animal food production.

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

- Carbetamide is a herbicide for grass weed control used at the time of sowing or immediately post-sowing.
- The product is intended only for professional use, and will not be available to the general public.
- No uses in the home garden are proposed.
- Intended for use as a pre-emergent herbicide for weed grass control.

c) *the toxicity of a substance*

- Low acute toxicity but moderate risk of producing irreversible toxicity.
- Non-genotoxic carcinogen.
- Category 1B developmental toxicant (according to Annex III inventory of ECHA) - may damage unborn child, toxic to aquatic life with long lasting effects, is harmful if swallowed and suspected of causing cancer.
- Dose related carcinogenicity and reproductive toxicity at high animal test doses.

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

- NIL

e) *the potential for abuse of a substance*

- NIL



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

- APVMA has controls in place over environmental concerns regarding toxicity.

*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; and (c) the toxicity of a substance.

In my view, the relevant parts of the SPF 2018 are the Scheduling Factors for Schedule 6 and Schedule 7 and the considerations for inclusion of a substance in Appendix B.

I have made a decision to amend the entry of carbetamide in the Poisons Standard, removing it from Appendix B and adding it to Schedule 6. In making my decision, I have taken into consideration new toxicological data that identifies hazards related to carcinogenicity and developmental toxicity that are consistent with its inclusion in Schedule 6.

Carbetamide is an approved active constituent available for use as an agricultural and veterinary (Agvet) chemical. The substance was included under Appendix B, Part 3 of the Poisons Standard in August 1991 as it did not meet the factors for inclusion in the Schedules based on the information available at that time. While there are currently no registered products containing carbetamide in Australia, the re-scheduling proposal has been submitted in support of a new herbicide product being assessed by the APVMA. Information presented with this current application supports that carbetamide presents a moderate to high health hazard, inconsistent with its current Appendix B entry.

I gave consideration to inclusion of carbetamide in Schedule 7 based on the adverse effects observed in carcinogenicity and developmental toxicity studies. Inclusion in Schedule 7 requires that a substance has high to extremely high toxicity and presents a severe hazard from repeated use that would result in a significant risk of producing irreversible toxicity. While the data were limited, both the European Chemicals Agency (ECHA) and the European Food Safety Authority (EFSA) have determined that carbetamide should be regarded as possibly carcinogenic and a potential developmental toxicant in humans. Concordant with these findings and that of the risk assessment undertaken by the applicant (APVMA), I agree with the Committee that these adverse effects occurred at high animal test doses and do not warrant a Schedule 7 listing. In coming to this conclusion, I have noted that:

- Carbetamide has been tested in a range of in vitro and in vivo genotoxicity assays, and found overall to be non-genotoxic.
- In the carcinogenicity studies in rats and mice, there were positive tumour responses in various tissues with an increased incidence of neoplastic lesions in both species. Several rare tumours were observed, including carcinomas, which occurred in different tissues (brain astrocytoma, liver cholangiocarcinoma and adrenal pheochromocytoma). The tumour incidences were all above the available historical control ranges. However, there was neither an effect on morbidity or mortality relative to concurrent controls nor was there any difference in tumour latency. The observation of rare tumours was restricted to high dose animals, and in the case of astrocytoma it was only observed among female rats. Moreover, carbetamide is considered to be a non-genotoxic carcinogen.
- In the 2-generation study in rats, no adverse effects on fertility or reproductive parameters were observed. In developmental toxicity studies in rats and rabbits, skeletal and visceral abnormalities (severe in the rat), delayed ossifications and post-implantations losses were observed at doses associated with minimal maternal toxicity e.g. slight reduction in maternal body weight gain. The maternal and developmental no-observed-adverse-effect-levels (NOAELs) in rat and rabbit were 450 and 40 mg/kg bw/day, respectively. These developmental effects were seen only at doses higher than those producing other effects noted in both short and long-term studies in the rat. Based on this information, I am satisfied that while carbetamide is of low

acute toxicity, it presents a moderate risk of producing irreversible toxicity that is consistent with a Schedule 6 entry.

On balance, I am satisfied that the weight of evidence supports that carbetamide meets the scheduling Factors for Schedule 6. While the acute oral and dermal toxicity in rats (> 2000 mg/kg bw and LD<sub>50</sub> >2000 mg/kg bw, respectively) is low and consistent with Schedule 5, the acute oral toxicity in mice (1718 mg/kg bw combined sex) is consistent with Schedule 6. I note that the acute inhalation toxicity LC<sub>50</sub> >380 mg/m<sup>3</sup>/4 hours) is consistent with Schedule. However, given there were no deaths and no clinical signs of toxicity at the maximum attainable concentration, I consider it is unlikely that the substance poses an inhalation risk.

In determining that carbetamide meets the requirements for listing under Schedule 6, I have also taken into account that this scheduling proposal is in support of a new Agvet product containing 900 g/kg carbetamide (as a water dispersible granule) that is intended for professional use only. The toxicological data for the formulated product, demonstrated that it has low acute toxicity via the oral, dermal and inhalation routes, is a slight eye irritant but not a skin irritant or skin sensitiser. Given the proposed use on broad care crops and the application methods (either by incorporation at sowing or post-sowing pre-emergence, using ground boom or aerial application methods), access to the formulated product by the general public for non-commercial use is highly unlikely. I am satisfied therefore that potential and reasonably foreseeable harm to professional users can be effectively addressed through the use of packaging and strong warning statements, as well as adherence to the conditions of use as recommended by the APVMA for inclusion on the product label. This is consistent with the requirements for inclusion in Schedule 6 and with controls on use of carbetamide products in other jurisdictions, particularly in the UK and Europe.

#### *Implementation date*

I have decided on an implementation date of **1 October 2020**.

## 2.2. Interim decision in relation to arbutin

### 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 arbutin as follows:

#### Schedule 6 – New entries

##### ARBUTIN (ALPHA) **except:**

- a) in preparations for application to the face containing 2 per cent or less alpha-arbutin with hydroquinone levels of 10mg/kg or less; or
- b) in preparations for application to the body containing 0.5 per cent or less alpha-arbutin with hydroquinone levels of 10mg/kg or less.

##### ARBUTIN (BETA) **except:**

- a) when included in Schedule 4; or
- b) in preparations for application to the face containing 7 per cent or less beta-arbutin with hydroquinone levels of 10mg/kg or less.

##### ARBUTIN (DEOXY OR OTHER DERIVATIVES).

#### Schedule 4 – New entry

ARBUTIN (BETA) in oral preparations except herbal preparations containing 500 mg or less beta-arbutin per recommended daily dose.

#### Index – New/Amended Entries

##### ARBUTIN (ALPHA)

Cross reference: ARBUTIN (BETA); ARBUTIN (DEOXY OR OTHER DERIVATIVES)

Schedule 6

##### ARBUTIN (BETA)

Cross reference: ARBUTIN (ALPHA); ARBUTIN (DEOXY OR OTHER DERIVATIVES)

Schedule 6

Schedule 4

##### ARBUTIN (DEOXY OR OTHER DERIVATIVES)

Cross reference: ARBUTIN (ALPHA); ARBUTIN (BETA)

Schedule 6

##### ARBUTIN

~~cross reference: HYDROQUINONE~~

### Appendix E, Part 3 – New entries

POISON	STANDARD STATEMENTS
ARBUTIN when included in Schedule 6.	A,G2,G3,E2,R2,S1
<p>A: 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>G2: If swallowed, give activated charcoal if instructed. (Note - the words 'at once' to be added to instruction A).</p> <p>G3: If swallowed, do NOT induce vomiting.</p> <p>E2: 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, or for at least 15 minutes.</p> <p>R2: If swallowed or inhaled, remove from contaminated area. Apply artificial respiration if not breathing. Do not give direct mouth-to-mouth resuscitation. To protect rescuer, use air-viva, oxy-viva or one-way mask. Resuscitate in a well-ventilated area.</p> <p>S1: If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.</p>	

### Appendix F, Part 3 – New entries

POISON	WARNING STATEMENTS	SAFETY DIRECTION
ARBUTIN when included in Schedule 6.	45	1,4
<p>1: Avoid contact with eyes</p> <p>4: Avoid contact with skin</p> <p>45: WARNING – If a pigmented spot or mole has recently become darker, changed colour, become enlarged or itchy, or bleeds, do not use this product, see your doctor immediately. Do not use on children. Do not use near the eyes. Mild irritation may occur; stop use if it becomes severe. If fading is not evident in three months, seek doctor's advice.</p>		

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

**1 October 2020**

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

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

- The [scheduling proposal](#) to amend the current Poisons Standard with respect to arbutin;
- Advisory Committee on Chemicals Scheduling's advice;
- The [public submissions](#) received in response to the [pre-meeting consultation](#);
- Section 52E of the *Therapeutic Goods Act 1989*, in particular (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 (f) any other matters that the Secretary considers necessary to protect public health;

- [Scheduling handbook: Guidance for amending the Poisons Standard](#); and
- [Scheduling Policy Framework](#) (SPF 2018).

*Summary of ACCS advice/recommendations to the Delegate*

The Committee recommended that new entries be created for arbutin (alpha, beta and deoxy or other derivatives) in Schedules 4 and 6 in the Poisons Standard as follows:

#### **Schedule 6 – New entries**

##### **ARBUTIN (ALPHA) except:**

- a) in preparations for application to the face containing 2 per cent or less alpha-arbutin with hydroquinone levels of 10mg/kg or less; or
- b) in preparations for application to the body containing 0.5 per cent or less alpha-arbutin with hydroquinone levels of 10mg/kg or less.

##### **ARBUTIN (BETA) except:**

- a) when included in Schedule 4; or
- b) in preparations for application to the face containing 7 per cent or less beta-arbutin with hydroquinone levels of 10mg/kg or less.

##### **ARBUTIN (DEOXY OR OTHER DERIVATIVES).**

#### **Schedule 4 – New entry**

**ARBUTIN (BETA)** in oral preparations except herbal preparations containing 500 mg or less beta-arbutin per recommended daily dose.

#### **Index – New/Amended Entries**

##### **ARBUTIN (ALPHA)**

Cross reference: ARBUTIN (BETA); ARBUTIN (DEOXY OR OTHER DERIVATIVES)

Schedule 6

##### **ARBUTIN (BETA)**

Cross reference: ARBUTIN (ALPHA); ARBUTIN (DEOXY OR OTHER DERIVATIVES)

Schedule 6

Schedule 4

##### **ARBUTIN (DEOXY OR OTHER DERIVATIVES)**

Cross reference: ARBUTIN (ALPHA); ARBUTIN (BETA)

Schedule 6

##### **ARBUTIN**

~~cross reference: HYDROQUINONE~~

### Appendix E, Part 3 – New entries

POISON	STANDARD STATEMENTS
ARBUTIN when included in Schedule 6.	A,G2,G3,E2,R2,S1
<p>A: 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>G2: If swallowed, give activated charcoal if instructed. (Note - the words 'at once' to be added to instruction A).</p> <p>G3: If swallowed, do NOT induce vomiting.</p> <p>E2: 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, or for at least 15 minutes.</p> <p>R2: If swallowed or inhaled, remove from contaminated area. Apply artificial respiration if not breathing. Do not give direct mouth-to-mouth resuscitation. To protect rescuer, use air-viva, oxy-viva or one-way mask. Resuscitate in a well-ventilated area.</p> <p>S1: If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.</p>	

### Appendix F, Part 3 – New entries

POISON	WARNING STATEMENTS	SAFETY DIRECTION
ARBUTIN when included in Schedule 6.	45	1,4
<p>1: Avoid contact with eyes</p> <p>4: Avoid contact with skin</p> <p>45: WARNING – If a pigmented spot or mole has recently become darker, changed colour, become enlarged or itchy, or bleeds, do not use this product, see your doctor immediately. Do not use on children. Do not use near the eyes. Mild irritation may occur; stop use if it becomes severe. If fading is not evident in three months, seek doctor's advice.</p>		

The Committee also recommended that the Chemicals scheduling delegate discuss the scheduling proposal with the medicines scheduling delegate given that the proposed amendment would impact medicines.

The Committee also recommended an implementation date of **1 October 2020**.

The reasons for the advice included:

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

- Benefits:
  - used as a skin whitening agent and treatment of conditions such as chloasma.
- Risks:
  - Potential for the hydrolysis of arbutin to hydroquinone and as a consequence cause exogenous ochronosis.

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

- Topical dermal use for skin whitening.
- Oral herbal use.

c) *the toxicity of a substance*

- Risk of skin pigmentation with long term use.
- Acute toxicity is consistent with schedule 6 scheduling factors.
- For deoxy arbutin there is insufficient information for a scheduling cut-off.

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

- NIL.

e) *the potential for abuse of a substance*

- NIL.

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

- Chemicals scheduling delegate to discuss the matter with the medicines scheduling delegate noting the previous discussion at the June 2019 meeting.

#### *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 (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 6.

I note that in September 2019 the medicine's delegate published an interim decision to create a new Schedule 4 entry for oral preparations of arbutin that excluded herbal preparations containing 500 mg or less of arbutin per recommended daily dose. My current decision will incorporate that interim decision and I will not be amending it further, other than to distinguish herbal preparations of arbutin in their beta form. The reasons below will focus on my decision to amend the current Poisons Standard by creating new Schedule 6 entries for the topical use of arbutin (alpha, beta and deoxy or other derivatives).

I have taken into consideration that arbutin when used as a topical skincare product as a skin-lightening agent for the prevention of melanin formation, acts via a therapeutic mechanism (tyrosinase inhibition). This means that the terminology "cosmetic creams/lotions" used in the scheduling proposal, are not appropriate given that products containing arbutin would meet the definition of a therapeutic good. In view of this, I have decided to omit this terminology in the Schedule 6 entries.

In assessing the safety profile of topical arbutin, I have given consideration to the toxicological data assessed by the European Commission's Scientific Committee on Consumer Safety (SCCS) on the topical use of alpha, beta and deoxy arbutins. I have decided to adopt the arbutin cut-offs detailed in the SCCS report for safe consumer use, as I find that they do not have the potential to release significantly relevant amounts of hydroquinone. I find that there is insufficient information for a scheduling cut-off for deoxy arbutin.

I consider that the main concern around the topical use of arbutin is the release of hydroquinone, which has the potential risk of causing hydroquinone induced-exogenous ochronosis and leukomelanoderma. Due to the potential risk of ochronosis and leukomelanoderma, alpha, beta and deoxy arbutins meet the Schedule 6 Scheduling Factors when above the exempted cut-offs. They present a moderate to high toxicity and a moderate risk of producing irreversible toxicity. This potential harm is reduced through the use of distinctive packaging with strong warnings and safety

directions on the label, with products supplied above the cut-off requiring Schedule 6 'Poison' labelling. I have decided to include warning statements, safety directions and first aid instructions which mirror those already outlined in the Poisons Standard for hydroquinone. I am satisfied that the weight of evidence supports that topical arbutin meets the scheduling Factors for Schedule 6. I note that should someone want to supply a topical product containing arbutin, it would be subject to assessment by the TGA, which would include an assessment of safety data. Scheduling could be reconsidered if warranted.

*Implementation date*

I have decided an implementation date of **1 October 2020** is appropriate.

I have made a decision to seek public comment on my interim decision in its totality. I have considered a request in the public submission for a separate implementation date of 1 June 2020 for the new Schedule 4 entry for arbutin-beta, to come into effect earlier than the other arbutin isomers under consideration. I have not identified evidence of an urgent public health need to justify an earlier implementation of 1 June 2020, as proposed in the public submission.



## 2.3. Interim decision in relation to aclonifen

### 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 aclonifen as follows:

#### Schedule 6 – New Entry

ACLONIFEN.

#### Index – New Entry

ACLONIFEN

Schedule 6

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

**1 October 2020**

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

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

- The [application](#) to amend the current Poisons Standard with respect to aclonifen;
- 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; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance;
- [Scheduling handbook: Guidance for amending the Poisons Standard](#);
- [Scheduling Policy Framework](#) (SPF 2018).

#### *Pre-meeting public submissions*

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

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

The Advisory Committee on Chemicals Scheduling recommended that a new Schedule 6 entry for aclonifen is created in the Poison Standard as follows:

#### Schedule 6 – New Entry

ACLONIFEN.

#### Index – New Entry

ACLONIFEN

Schedule 6

The reasons for the advice included:

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

- Herbicide for wheat, barley, triticale crops with risks managed by suitable labelling for PPE.
- Not for the domestic market.

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

- Herbicide intended for use in broad acre crops, thus low risk of general public exposure.

c) *the toxicity of a substance*

- Low acute toxicity, no skin or eye toxicity (slight irritant).
- Sensitiser potential in GPMT (most animals).
- Carcinogenicity without genotoxicity potential.

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

- NIL.

e) *the potential for abuse of a substance*

- NIL.

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

- NIL.

*Reasons for interim decision*

I agree with the Committee's 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; and (c) the toxicity of a substance.

In my view, the relevant parts of the SPF 2018 are the Scheduling Factors for Schedule 5, Schedule 6 and Schedule 7.

I have made a decision to create a new Schedule 6 entry for aclonifen. In making my decision I have taken into account data demonstrating that aclonifen is a skin sensitiser and is a non-genotoxic carcinogen.

Aclonifen is a new nitro diphenylether herbicide. While there is currently no product application associated with the active constituent, the APVMA has confirmed that a submission for an end-use product for use in broad acre situations is anticipated.

Concordant with the Scheduling Factors for inclusion in Schedule 5, aclonifen is of low acute oral ( $LD_{50} > 5000$  mg/kg bw), dermal ( $LD_{50} > 5000$  mg/kg bw), and inhalation toxicity ( $LC_{50} > 5069$  mg/m<sup>3</sup>/4h), is not a skin irritant and is a slight eye irritant in rabbits, with symptoms exhibited in one test animal resolving within 48 hours. There is no evidence of developmental toxicity (up to up to 25 mg/kg/d in rabbits), reproductive toxicity, or genotoxic potential in an acceptable range of in vivo and in vitro assays. However, aclonifen caused overt skin sensitisation in the maximisation test in guinea pigs (GPMT), consistent with Schedule 6. There was also evidence of a potential for aclonifen to bind chromatin, and thus has a theoretical potential to induce changes in DNA expression.

While the toxicity of aclonifen is less than that of other chemicals in the same class, I considered whether, based on the carcinogenicity concerns and the uncertainty around the mode of action (MOA), aclonifen poses a moderate or high health hazard from repeated use and a moderate or high risk of producing irreversible toxicity. I find that aclonifen presents a moderate hazard from repeated use and a moderate risk of producing irreversible toxicity, consistent with a Schedule 6 entry. Importantly, there was only a single study showing an increased incidence of a rare tumour (astrocytoma) in rats. I have noted that the EU has classified aclonifen with the risk phrase R40, '*Limited evidence of a carcinogenic effect*', on the basis of the unresolved origin of the malignant astrocytomas in female rats and the uncertainty regarding the comparability of rats and humans in this respect. I have also given weight to the fact that the acute toxicological data does not support

that aclonifen presents high to extremely high toxicity and there was no evidence to support that it has a high potential for causing harm at low exposures.

While aclonifen poses a moderate hazard from repeated use and a moderate risk of producing irreversible toxicity, these risks are manageable. The APVMA has confirmed that the management of health risks associated with pesticide use is achieved primarily via label directions, established from a consideration of the acute hazards of the product in conjunction with possible adverse health effects from repeated exposure to both workers and the general-public. In assessing the risk to users of products containing aclonifen or people consuming crops that have been treated with aclonifen, the APVMA applies a margin of exposure (MOE) of 100 to the No Observed Adverse Effect Level (NOAEL). As products containing aclonifen are neither intended to be made available directly to members of the public, nor are they intended for use in areas with ready public access, I am satisfied that the pesticide regulator (APVMA) will be able to manage the risks from exposure to products containing aclonifen.

Having considered all available information, I am satisfied that on balance, the evidence supports that a Schedule 6 entry with no concentration cut-off is appropriate for aclonifen.

*Implementation date*

I have decided on an implementation date of **1 October 2020**.

## 2.4. Interim decision in relation to picramic acid (including its salts)

### 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 picramic acid (including its salts) as follows:

#### Schedule 6 – New Entry

PICRAMIC ACID including its salts (excluding other derivatives) **except** when used in hair dye products at a concentration of 0.6 per cent or less of picramic acid after mixing for use when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin allergy to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height.

#### Appendix E, Part 1 – New Entry

Standard Statements:

A For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once); and

E1 If in eyes wash out immediately with water.

#### Appendix F, Part 2 – New Entries

Safety Directions – General:

5 Wear protective gloves when mixing or using.

Warning Statements

28 Repeated exposure may cause sensitisation.

#### Index – New Entry

**PICRAMIC ACID (including its salts)**

CROSS-REFERENCE: 2-amino 4 6 dinitrophenol

Schedule 6

Appendix E, Part 1

Appendix F, Part 2

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

**1 June 2021**

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

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

- The [application](#) to amend the current Poisons Standard with respect to picramic acid and its salts;
- Advisory Committee on Chemicals Scheduling's advice;

- The [public submissions](#) received in response to the pre-meeting consultation;
- 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; and (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance;
- [Scheduling handbook: Guidance for amending the Poisons Standard](#); and
- [Scheduling Policy Framework](#) (SPF 2018).

*Summary of ACCS advice/recommendations to the Delegate*

The Advisory Committee on Chemicals Scheduling recommended that new Schedule 6, Appendix E and Appendix F entries for picramic acid (including its salts) in the Poisons Standard as follows:

### **Schedule 6 – New Entry**

**PICRAMIC ACID including its salts (excluding other derivatives) *except* when used in hair dye products at a concentration of 0.6 per cent or less of picramic acid after mixing for use when the immediate container and primary pack are labelled with the following statements:**

**KEEP OUT OF REACH OF CHILDREN, and**

**WARNING – This product contains ingredients which may cause skin allergy to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.**

**written in letters not less than 1.5 mm in height.**

### **Appendix E, Part 1 – New Entry**

Standard Statements:

**A For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once); and**

**E1 If in eyes wash out immediately with water.**

### **Appendix F, Part 2 – New Entries**

Safety Directions – General:

**5 Wear protective gloves when mixing or using.**

Warning Statements

**28 Repeated exposure may cause sensitisation.**

### **Index – New Entry**

**PICRAMIC ACID (including its salts)**

**CROSS-REFERENCE: 2-amino 4 6 dinitrophenol**

**Schedule 6**

**Appendix E, Part 1**

**Appendix F, Part 2**

The Committee also recommended an implementation date of **1 June 2021**.

The reasons for the advice included:

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

- Benefits
  - Sodium picramate, a non-reactive dye used as a direct hair colouring agent in many hair dye products.
- b) *the purpose for which a substance is to be used and the extent of use*
  - The chemicals are used in cosmetics, colourants and in hair dye products of up to a maximum concentration of 0.6%.
  - The chemicals are also reported to be used for dyeing fur and in pyrotechnics.
- c) *the toxicity of a substance*
  - Picramic acid and its salt are reported to be sensitising to the skin and reported to be toxic to the male reproductive system.
- d) *the dosage, formulation, labelling, packaging and presentation of a substance*
  - NIL.
- e) *the potential for abuse of a substance*
  - NIL.
- f) *any other matters that the Secretary considers necessary to protect public health*
  - NIL.

*Reasons for 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; and (c) the toxicity of a substance.

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

I have made a decision to create new Schedule 6, Appendix E and Appendix F entries for picramic acid (including its salts). In making my decision, I have taken into account the potential harms including skin sensitisation, arising from use of these substances in hair dye products.

Picramic acid and its salt, sodium picramate are used in hair colouring formulations up to a maximum concentration of 0.6%. While both substances are used in hair dyes, as the acid dissociation constant (pKa) of picramic acid is around 4, it is always the sodium picramate which is available in typical hair dye formulations (pH 6.5 - pH 10).

The main toxicological concern with these substances is skin sensitisation. Based on mouse local lymph node assay (LLNA) data, picramic acid and its salts are moderate skin sensitisers with the estimated concentration needed to produce a threefold increase in lymphocyte proliferation (EC3) determined to be 6.7 %. As moderate skin sensitisers, picramic acid and sodium picramate meet the SPF 2018 Scheduling Factors for inclusion in Schedule 6. The substances are also acutely toxic via all routes of exposure; harmful following chronic oral exposure at low concentrations in animal studies; and are toxic to the reproductive system, particularly in males, based on testicular damage observed in rats. In an acute oral toxicity study, the calculated LD50 of picramic acid was 110 mg/kg bw which is consistent with Schedule 6 (between 50 mg/kg – 2000 mg). I note also that the margin of safety (MOS) of 155, derived from the dermal absorption (1.12 µg/cm<sup>2</sup>) and 90-day repeat dose study (5 mg/kg bw/day) in rats, is not far above the threshold generally considered safe (MOS of 100) for use in cosmetics.

Material to my decision to include a maximum concentration cut-off of 0.6 per cent to unscheduled are the recommendations made in the report on picramic acid and sodium picramate by the [European Scientific Committee on Consumer Safety](#) (SCCS 2012). The SCCS is of the opinion that the use of picramic acid/sodium picramate, with a maximum on-head (i.e. what is administered on the head) concentration of 0.6% in oxidative and non-oxidative hair dye formulations, does not pose a risk to the health of the consumer, apart from its sensitising potential. I have taken into account that

in Canada, sodium picramate is listed on the Cosmetic Ingredient Hotlist- List of Ingredients that are Restricted for Use in Cosmetic Products, with the maximum concentration permitted of 0.1%. However, I am satisfied that on balance, a concentration cut-off of 0.6% is protective based on the use patterns of products containing picramic acid and its salts and the likely toxicity end point of concern being skin sensitisation. While not material to my decision, I note that a concentration cut-off of 0.6% is also consistent with the Association of Southeast Asian Nations (ASEAN) cosmetic directive that specifies a concentration of 0.6 % applied to the head under oxidative conditions with appropriate warning labels.

In assessing the safety profile, I agree with the Committee's advice that picramic acid and its salts clearly present a risk to consumers when used in hair dye products at concentrations greater than 0.6%. Based on the information provided, I am satisfied that the potential risks can be controlled by mandating concentration restrictions and warning labels using an appropriate Schedule 6 entry. This Schedule 6 entry is consistent with other sensitising hair dyes that have previously been considered for inclusion in the Poisons Standard. Restricting the concentration exemption for picramic acid at its salts in hair dye products will also serve to mitigate any potential risk arising from repeated exposure.

#### *Implementation date*

In deciding on an appropriate implementation date, I have taken into consideration concerns raised in the public submissions that a minimum 12-month adequate transition period is required by industry to allow for compliance with any labelling and/or reformulation changes. As no immediate health signals have been identified, in order to minimise regulatory burden, I have decided on an implementation date of **1 June 2021**.

### 3 Interim decisions on proposed amendments referred to the Advisory Committee on Medicines and Chemicals Scheduling in joint session (Joint ACMS-ACCS #24, March 2020)

#### 3.1. Interim decision in relation to marker dyes and pigments

##### 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 marker dyes and pigments as follows:

##### **Part 1 of the Poisons Standard, Interpretation – New Entry**

**“Marker dyes or pigments”** means any product that is added to a liquid used in agricultural or veterinary chemicals to identify or distinguish treated from untreated objects, land or organisms by temporarily imparting colour on the relevant object, land or organism through, for example, spot – or boom-spraying.

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

**1 October 2020**

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

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

- The [scheduling proposal](#) to amend the current Poisons Standard with respect to marker dyes and pigments;
- Joint Meeting of the Advisory Committee on Chemicals Scheduling and the Advisory Committee on Medicines Scheduling’s advice; and
- The [public submissions](#) received in response to the [pre-meeting consultation](#).

##### *Summary of Joint ACCS-ACMS advice/recommendations to the Delegate*

The Joint Meeting of the Advisory Committee on Medicines Scheduling and the Advisory Committee on Chemicals Scheduling recommended that a new entry for marker dyes and pigments in the Poisons Standard as follows:

##### **Part 1 of the Poisons Standard, Interpretation – New Entry**

**“Marker dyes or pigments”** means any product used to temporarily impart colour to:

- i) an agricultural chemical intended for spot- or boom -spraying to detect missed spots or to avoid spraying a plant or area multiple times; or
- ii) a veterinary chemical for the purpose of identifying treated or selected animals.

The Committee also recommended that the Delegate go out for further consultation with key stakeholders with regards a suitable definition based on the amendments proposed above.

The Committee recommended that an implementation date was not relevant.

Members agreed that as this item relates to Part 1 of the SUSMP, rather than to an actual substance, assessment of the Section 52E criteria was not required.

##### *Reasons for interim decision*

I agree with the Committee’s finding that the provisions of section 52E of the *Therapeutic Goods Act 1989* do not apply in this situation as the item relates to Part 1 of the Poisons Standard only.



I have made a decision to amend the Poisons Standard to include an explicit definition of 'marker dyes and pigments' in Part 1, Interpretation. In making this decision, I find that there is a lack of clarity with regards the scheduling of pigments and marker dyes used in the agricultural and veterinary (agvet) sectors as these substances are not covered by the existing Poisons Standard definition of 'paints and tinters'.

Marker dyes and pigments are widely used in animal and plant industries to assist in the identification of treated versus untreated objects, land or organisms. They are also used to give colour to baits and fertilisers and to identify different cultivars of seeds and different individual animals. Advice from the APVMA is that there are several categories of agricultural and veterinary marker dyes and pigments and that there are also a range of products where colour is either included as part of a product's formulation with other actives or are standalone products that are purely dye markers designed to be added to a product to help the farmer/contractor see where they have sprayed or not. Historically, many of these chemicals have been considered under paints and tinters.

I am satisfied, however, that pigments and marker dyes are not paints. Paints, as per the definition in the Poisons Standard, are substances applied as a colouring or protective coating to a surface. In contrast, agvet pigments and marker dyes are added to a liquid that is subsequently applied to a surface (inert or living) to aid identification of the application of that liquid.

In determining the scope of for a definition for marker dyes and pigments in the Poisons Standard, I have taken into consideration that that these substances have many specific and niche uses both within and outside of the agvet space. I have also taken into account public submissions from three peak industry bodies representing agvet products and human hygiene products indicating in principle support for a definition for pigments and marker dyes in the Poisons Standard. These submissions, while seeing value in a clear definition of marker dyes and pigments used in animal and plant industries, raised concerns around the scope of the definition and the terminology used. To minimise risk and avoid confusion, I have determined that it is appropriate that the scope of the definition be specific to agvet situations and restricted to covering a limited range of uses with similar exposure conditions. A potential risk highlighted in the public submissions was that the use of the term '*any substance*' in the proposed definition could result in substances being applied post-registration to agricultural chemicals which are not appropriate for use on potential food crops. To address this, I have decided, to replace the term '*any substance*' with '*any product*'.

I have also given consideration to whether or not 'marker dyes and pigments' should have a specific cross reference in the Index of the Poisons Standard, identifying the specific marker dyes and pigments capture by the proposed definition. However, I agree with the Committee that cross-referencing in the Index is not appropriate and that uses should be restricted to creating exceptions from a schedule entry, noting that these are not generally cross-referenced.

I note that while the Poisons Standard currently includes references to 'hair dye' products, 'dyeing of eye lashes and eyebrows', 'azo dyes' and a number of dyes which are specifically named, there is currently no explicit definition for 'hair dyes' or 'dyeing' in Part 1 of the Poisons Standard. Given the variety of situations in which pigments and dye markers are used, I am satisfied that it is appropriate to include an explicit definition for these chemicals when used in agvet situations. The creation of a definition for agvet pigments and marker dyes does not exempt these substances from scheduling and does not alter any current substance entries in the Poisons Standard. The definition will however, provide clarity to industry stakeholders and facilitate compliance with the legislative framework that the APVMA, as the relevant government regulator, administers and to the requirements of the Poisons Standard.

#### *Implementation date*

I have decided that an implementation date of **1 October 2020** is appropriate.

## 3.2. Interim decision in relation to nicotine (heated tobacco products)

### 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 nicotine as proposed in this application, that is, to exempt nicotine in tobacco prepared and packed for heating from Schedule 7.

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

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

- The [application](#) to amend the current Poisons Standard with respect to nicotine;
- Joint Meeting of the Advisory Committee on Medicines Scheduling and the Advisory Committee on Chemicals Scheduling's advice as required by sub-section 52E(3) of the *Therapeutic Goods Act 1989*;
- The [public submissions](#) received in response to the [pre-meeting consultation](#);
- As required by sub-section 52E(1) 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;
- [Scheduling Policy Framework](#) (SPF 2018) as required by sub-section 52E(2);
- [Scheduling handbook: Guidance for amending the Poisons Standard](#);
- [World Health Organisation Heated tobacco products \(HTPs\) market monitoring information sheet](#);
- [PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes](#); and
- [FDA News Release dated 30 April 2019: FDA permits sale of IQOS Tobacco Heating System through premarket tobacco product application pathway](#).

#### *Summary of Joint ACCS-ACMS advice/recommendations to the Delegate*

The reasons for the advice included:

The Joint Meeting of the Advisory Committee on Chemicals Scheduling and the Advisory Committee on Medicines Scheduling recommended that the current scheduling of nicotine remains appropriate as there is insufficient evidence to support an exemption from Schedule 7 for nicotine in heated tobacco products (HTPs).

Members noted that the relevant matters the Secretary is required to consider by subsection 52E(1) of the *Therapeutic Goods Act 1989* include (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 matters considered by the committee under subsection 52E(1) include:

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

- The Committee did not identify any benefits of the use of nicotine when in tobacco when prepared and packed for heating, advising that the available evidence does not support that

HTPs are a safer alternative to traditional tobacco products. The Committee identified the following risks:

- Nicotine addiction either for new users of HTPs or new or continuing users of nicotine in tobacco prepared and packed for smoking.
- Re-normalising smoking especially among young people who would otherwise be at low risk of initiating nicotine addiction.
- Insufficient evidence regarding the nature of any risk of long-term use. HTPs contain harmful and potentially harmful constituents.
- Risk of accidental exposure to children.

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

- The Committee identified the purpose for which nicotine when in tobacco when prepared and packed for heating as a new nicotine-delivery device for the non-therapeutic use of tobacco.

c) *the toxicity of a substance*

- The Committee noted the following in relation to the toxicity of nicotine when in tobacco when prepared and packed for heating:
  - In vitro data indicates that HTP aerosol can be cytotoxic and mutagenic, can produce pathophysiological changes in human tissues.
  - The response produced by HTP aerosol is similar to that produced by cigarette smoke with respect to the development of precancerous lesions such as hyperplasia and squamous metaplasia in the respiratory tract epithelium.
  - On scientific and toxicological grounds nicotine when in tobacco when prepared and packed for heating meets Schedule 7 factors – that is it has a high to extremely high toxicity, presents a high health hazard, requires special precautions for handling, and has a high potential for causing harm at low exposure.

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

- The Committee advised that:
  - Nicotine when in tobacco when prepared and packed for heating functions by way of reconstituted tobacco leaf and excipients heated and consumed via inhalation.
  - An HTP delivers comparable levels of nicotine as conventional combustible tobacco products.

e) *the potential for abuse of a substance*

- The Committee advised that nicotine when in tobacco when prepared and packed for heating when used as intended carries a high risk of dependence.

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

- The Committee advised that the current pathway for approval to supply products for smoking cessation is available for an HTP. An application for registration on the ARTG could be made, which would involve assessment of the safety, efficacy and quality by the TGA, consistent with the requirements for existing nicotine replacement products.

*Reasons for interim decision*

I have made a decision not to amend the current scheduling of nicotine in the Poisons Standard, specifically, not exempt from Schedule 7 nicotine when in tobacco when prepared and packed for heating. In making my decision, I agree with the Committee that the most relevant parts of the SPF 2018, for the application for exemption of nicotine when in tobacco when prepared and packed for heating from Schedule 7, are the Scheduling Factors for Schedule 7, which currently captures nicotine in HTPs. Schedule 7 substances have a high to extremely high toxicity, present a high

health hazard, require special precautions for handling, and have a high potential for causing harm at low exposure.

I also note the guidance in the Scheduling Handbook on the principle of 'reasonable safety' when assessing whether a substance is suitable for exemption from scheduling. Although the principle of reasonable safety is framed within the context of medicine scheduling, there are a number of relevant matters regarding the risks and benefits from wider availability for consumers.

I agree with the Committees view 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. I also note the Committee's view that the purpose of HTPs is to provide a new nicotine-delivery device for non-therapeutic use of tobacco.

Having considered the Applicant's proposal, including the data provided with the application, I find that there are significant safety concerns with HTPs, notably as identified by the Committee, the various risks of use of nicotine when in tobacco when prepared and packed for heating, its toxicity and the potential for abuse with no demonstrated benefit of its use. In this regard, I consider that the Applicant's focus on using tobacco cigarettes as a relevant comparator is too narrow and does not fully reflect the matters I am required to take into account, under subsection 52E(1), when making a decision to amend the Poisons Standard.

In my assessment of the literature, I have not identified compelling evidence to establish a public health benefit from greater access to nicotine in HTPs. My views are consistent with the Committee's advice, in which a number of risks were identified with no clear, substantiated benefits. The available data indicate that HTPs contain toxic compounds including carcinogens and that HTPs aerosol can be cytotoxic and mutagenic and, can potentially produce pathophysiological changes in human tissues comparable to those produced by cigarette smoke. Independent researchers<sup>1</sup> analysing data that Philip Morris provided to the US FDA in support of marketing of their IQOS HTP product found no statistically detectable difference between IQOS and conventional cigarettes for 23 of the 24 non-cancer biomarkers of potential harm measured in Americans, and 10 of 13 measured in Japanese.

I consider that nicotine presents a severe hazard from repeated use leading to potential addiction and a significant risk of producing irreversible toxicity, which may involve serious, acute or chronic health risks or death. In this regard, I note that the application, if agreed, would exempt nicotine when in tobacco when prepared and packed for heating from all regulation as a poison. I am not persuaded that HTPs would not attract 'never smokers' including youth. Further, I am satisfied that HTPs can expose users long term to a range of known and unknown toxicants. I am not satisfied that the dosage, formulation, packaging and presentation of nicotine in HTPs mitigates the risk profile of nicotine such as to warrant a less restrictive scheduling classification than is currently in place.

I also note the information provided by the NSW Poisons Information Centre (NSW PIC) in their submission. The NSW PIC manage approximately half of Australia's poisons-related calls. Of particular relevance, I note that the NSW PIC reported that over 82% of calls relating to tobacco exposures were accidental paediatric exposures. I agree with the concerns raised by NSW PIC that HTPs may increase the risk of exposure to greater quantities of tobacco in accidental paediatric exposures.

Harm reduction has been cited by the Applicant and in public submissions advocating for the scheduling proposal, with these submissions also claiming that HTPs are another harm reduction tool, similar to nicotine replacement therapy products. However, I did not identify compelling evidence in support of these claims. Existing nicotine replacement products are therapeutic goods that require approval by the TGA in order to be supplied in Australia. Further, unlike HTPs, existing smoking cessation pharmacotherapies (including nicotine replacement therapies) included on the

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<sup>1</sup> PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6202159/>

ARTG have an established safety profile and have been shown to be effective for the purposes of smoking cessation.

In making my decision I have also considered the firm opposition to down-scheduling nicotine in HTPs expressed by many peak health bodies and State and Territory Health Departments. Of the thirty-six (36) submissions received in total, twenty-three (23) submission were opposed the scheduling proposal including those from: The ACT Health Department, The Royal Australian College of General Practitioners, The Stroke Foundation, The Cancer Council Australia, The National Heart Foundation of Australia, The Australian Council on Smoking and Health, The Pharmaceutical Society of Australia, The Australian Medical Association, and The Pharmacy Guild of Australia among others. I note the strong concerns raised in these submissions; that the wide availability of HTPs would carry significant public health risks and that claims of relative safety have not been substantiated.

I have considered the regulatory status of HTPs internationally and the guidance from the WHO<sup>2</sup>. I note, that in the US HTPs are not Food and Drug Administration (FDA)-approved, which is a requirement for a tobacco product to be marketed with reduced exposure or risk claims. Further, the FDA has confirmed that all tobacco products are potentially harmful and addictive and have recommended that people who do not currently use them should continue not to use them.<sup>3</sup>

I am not satisfied that there is a net public health benefit from wider availability of nicotine in the form of HTPs. I do not consider that HTPs would make a significant contribution to population harm reduction if I agreed to amend the Poisons Standard as proposed in the application. I consider that maintaining the current scheduling for HTPs is necessary to protect public health from the risks associated with introducing a new nicotine product for non-therapeutic use. I note that the current pathway to supply Schedule 4 nicotine products for smoking cessation is available for HTPs. An application for registration on the ARTG could be made, which would involve assessment of the safety, efficacy and quality by the TGA, consistent with the requirements for existing nicotine replacement products.

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<sup>2</sup> WHO Heated tobacco products (HTPs) market monitoring information sheet

[https://www.who.int/tobacco/publications/prod\\_regulation/htps-marketing-monitoring/en/](https://www.who.int/tobacco/publications/prod_regulation/htps-marketing-monitoring/en/)

<sup>3</sup> FDA permits sale of IQOS Tobacco Heating System through premarket tobacco product application pathway, dated 30 April 2019

<https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway>

### 3.3. Interim decision in relation to pentobarbital

#### 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 pentobarbital as follows:

#### Appendix D, Item 9 – New entry

9.	<b>Poisons which must be stored in a locked container to prevent unauthorised access</b>
	PENTOBARBITAL in injectable preparations.

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

1 October 2020

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

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

- The [scheduling proposal](#) to amend the current Poisons Standard with respect to pentobarbital;
- Joint Meeting of the Advisory Committee on Medicines Scheduling and the Advisory Committee on Chemicals Scheduling's advice;
- The [public submissions](#) received in response to the [pre-meeting consultation](#);
- 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;
- [Scheduling Policy Framework](#) (SPF 2018);
- [Scheduling handbook: Guidance for amending the Poisons Standard](#);
- [The National Coronial Information System \(NCIS\) report on pentobarbital-related deaths in Australia 2000 – 2017](#); and
- Specialist advice on veterinary medicine from two veterinary surgeons.

#### *Summary of Joint ACCS-ACMS advice/recommendations to the Delegate*

The reasons for the advice included:

The Committee considered that the proposal to move pentobarbital into Schedule 8 was not appropriate. The Committee recommended that the delegate, in consultation with States and Territories, consider whether appropriate controls on storage and access could be achieved by including a new entry in Appendix D. The objective would be to standardise the controls applied to the storage and access of Schedule 4 pentobarbital across the jurisdictions, acknowledging that not all jurisdictions adopt that Appendix by reference at present. A suitable outcome is that pentobarbital injection must be stored in a manner that precludes unauthorised access.

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:

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

- Risks:
  - Death from misuse/suicide.
  - Rapidly fatal and an attractive method promoted by suicide/voluntary euthanasia groups.
- Benefits:
  - a cheap and effective agent for humane animal euthanasia.

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

- Currently marketed pentobarbital injection products are only for animal euthanasia and are widely and successfully used for this purpose, both by veterinary surgeons and by other trained and authorised persons, such as wildlife carers.
- Used widely in veterinary practice for euthanasia of animals.
- Used in the euthanasia of wild animals

c) *the toxicity of a substance*

- Narrow therapeutic index, consistent with inclusion in Schedule 4.
- Rapid acting, causing profound central nervous system and respiratory depression and death (as little as 2g i.e. 6 mL of 325 g/L pentobarbital). Much more toxic than benzodiazepines.

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

- Risks from pentobarbital in injectable form may be different to risks associated with oral forms.
- No products listed on the ARTG for human use.
- Pentobarbital products available for animal euthanasia. Comes in large containers 500mL, however smaller pack sizes are also available.

e) *the potential for abuse of a substance*

- Misuse for suicide reported but no evidence of abuse of injectable pentobarbital as a recreational drug.
- Oral forms, which are already Schedule 8, were previously associated with a well-defined withdrawal syndrome following prolonged use and were also quite widely used recreationally in the past.
- Potential for misuse for the purpose of suicide. Theoretically potential for recreational use however few reports of this.

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

- The current controls on storage and access should be improved and standardised across the States and Territories, to prevent unauthorised access.
- The Delegate should explore other mechanisms for achieving additional controls under a Schedule 4 entry.
- Recommend the Delegate consider an Appendix D entry, noting that not all State and Territories adopt by reference.

### *Reasons for interim decision*

I have made an interim decision to retain the Schedule 4 entry for injectable pentobarbital. I have also decided to amend the current Poisons Standard to clarify the storage requirements for Schedule 4 injectable pentobarbital through the provision of a new Appendix D listing. The detailed reasons for my decision follow.

It is my view that a Schedule 4 classification for injectable pentobarbital is appropriate. I am not persuaded that moving injectable pentobarbital to Schedule 8 will reduce the risk of this substance being used as a method of suicide in individuals associated with the veterinary industry or by members of the general public. In coming to this decision, I had particular regard for new evidence presented since the previous consideration of pentobarbital in November 2016. These included the National Coronial Information System (NCIS) report on pentobarbital-related deaths in Australia 2000 – 2017 (which will be referred to as the 'NCIS report'), the public submissions in response to the pre-meeting consultation for the current scheduling consideration of injectable pentobarbital and the specialist advice on veterinary medicine provided by two veterinary surgeons.

I initiated the review on the scheduling of injectable pentobarbital on the recommendation of the South Australian Coroner, dated 23 October 2019, following an [inquest into two deaths associated with pentobarbital](#). I note that the inquest was in large part devoted to exploring measures to prevent the use of pentobarbital as a method of suicide in individuals associated with the veterinary industry. I recognise that my interim decision is contrary to Coroner's recommendation. I will set out my detailed reasons below.

I want to recognise the value of human life and the critical importance of preventing suicide. It is my view that a Schedule 8 classification is unlikely to prevent access to this substance by persons who might be associated with veterinary establishments, at least as far as that method of suicide is concerned. The storage of pentobarbital injectable solution in a drug safe, required for Schedule 8 substances, is likely to preclude access by unauthorised persons. However, a Schedule 8 classification will not necessarily preclude access by veterinary surgeons themselves or, in some States and Territories, by veterinary nurses, animal control officers and approved personnel in wildlife care groups. For these groups, inclusion of pentobarbital in Schedule 8 adds regulatory burden but does not necessarily have any impact on their risk of choosing to use this substance for the purpose of suicide.

I agree with the advice from the Joint ACMS-ACCS that record keeping in a Schedule 8 register is inherently less robust where bulk liquid forms of these medicines are being recorded, compared to divided doses such as tablets or ampoules. I have considered the scenario that it is unlikely that the small volume of pentobarbital required to be consumed to induce death in a human, can be missed in the commonly used 500 mL multi-dose vial. These large volume, multi-use vials are necessary to accommodate dosage volumes for small (<1 kg) to large (> 400 kg) animals, and when a number of animals must be euthanised promptly. On balance, I find that Schedule 8 restrictions on injectable pentobarbital is unlikely to prevent the use of pentobarbital as method of suicide in individuals associated with the veterinary industry.

In making my decision, I have attached significant weight to the evidence in the NCIS report, which establishes that the major source of pentobarbital used in suicides was not from veterinary establishments. The NCIS report demonstrates that the majority of the deceased were not from people working within veterinary or animal establishments or the general public acquiring pentobarbital from these establishments in Australia.

A number of possible unintended consequences would result from the inclusion of liquid pentobarbital in Schedule 8. I find that the benefit of having detailed record keeping requirements for pentobarbital and regular inventories under a Schedule 8 classification does not outweigh the need for timely access to this substance. It is my view that the added record keeping requirements and obligatory containment of pentobarbital in a drug safe when not in use, will negatively impact the ability for professionals such as: veterinary surgeons and their staff; researchers who utilise laboratory animals; government and non-government officers working with wildlife and domestic animal control; and officers managing dog health programs in remote aboriginal communities, to carry out their duties effectively and humanely. I find the specialist advice on veterinary medicine



from the two veterinary surgeons to be of particular relevance on this matter. On balance, I find that the storage and record keeping requirements associated with Schedule 8 would add considerable regulatory burden for professionals using pentobarbital without any demonstrable reduction in the incidence of pentobarbital-related suicide.

I will now set out my reasons for retaining the Schedule 4 entry for injectable pentobarbital. In my reading of the available data, pentobarbital has a narrow therapeutic index and carries a significant risk of respiratory depression, even at the doses previously used therapeutically in humans. These factors are consistent with a Schedule 4 classification, which are currently in place. On balance, I am not satisfied that, misuse of pentobarbital injection for suicidal purposes, by itself, meets the Scheduling Factors under Schedule 8.

I have made a decision to include a specific requirement for the storage of injectable pentobarbital in a locked container to prevent unauthorised access. I understand that such controls are broadly in place through the provision of Section 3 of the Poisons Standard, which requires person who sells or supplies Schedule 4 (or Schedule 3) poisons to keep those poisons in a part of the premises to which the public does not have access. I recognise that the implementation of this storage requirement is inconsistent across the States and Territories insofar as it relates to injectable pentobarbital. It is my view that an Appendix D entry will clarify the specific storage requirements for injectable pentobarbital and encourage States and Territories to adopt standardised controls, without the additional burden of the record keeping requirements associated with Schedule 8. As far as veterinary premises other than veterinary hospitals is concerned, I understand that there is variation in how the storage practices within these facilities are governed across the jurisdictions. In accordance with the legislative powers of the Poisons Standard, the particulars relating to the implementation and regulation of these storage requirements to any premises, veterinary or otherwise, be it a veterinary hospital or other type of veterinary clinic is a matter for the States and Territories.

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; (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.

#### *Implementation date*

I have decided that an implementation date of **1 October 2020** is appropriate.