Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

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

26 July 2024

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

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

- the interim decisions made by a delegate of the Secretary under regulation 42ZCZN in relation to proposed amendments to the current Poisons Standard which were referred to an expert advisory committee[1] under subdivision 3D.2 of the Regulations in March 2024;
- 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 **23 August 2024**.

Submissions should be provided through our consultation hub. Submissions will be considered by the Delegate in making the final decision.

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

Defined terms

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

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

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

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

Interim decisions on proposed amendments referred to the Advisory Committee on Medicines Scheduling (ACMS #44, March 2024)

Interim decision in relation to cytisine

Proposal

The Delegate received an application to create new Schedule 2 and 4 entries for cytisine. The proposed amendment would include cytisine in divided preparations for oral use containing 1.5 mg or less of cytisine per dosage unit in Schedule 2, and all other preparations containing cytisine in Schedule 4. Cytisine is currently an unapproved ingredient in preparations for therapeutic use.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to create new entries for cytisine in Schedules 3 and 4 as follows:[2]

Schedule 4 – New entry

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

Schedule 3 – New entry

CYTISINE in divided oral and oromucosal preparations with a recommended daily dose of 9 mg or less of cytisine as an aid in withdrawal from tobacco smoking in adults.

Index – New entry

CYTISINE

Schedule 4
Schedule 3

Materials considered

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

- The application to amend the current Poisons Standard with respect to cytisine (the Application)
- The 41 public submissions, received in response to the pre-meeting public consultation (the Submissions)
- The advice received from the 44th meeting of the Advisory Committee on Medicines Scheduling (the Committee)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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 SPF, and

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

- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that new entries for cytisine be created in the Poisons Standard as follows:[3]

Schedule 4 – New entry

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

Schedule 3 – New entry

CYTISINE in divided oral and oromucosal preparations with a recommended daily dose of 9 mg or less of cytisine for the treatment of nicotine dependence in adults.

Index – New entry

CYTISINE

Schedule 4
Schedule 3

The Committee recommended an implementation date of **1 October 2024**, to avoid any unnecessary delay to industry.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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:

- Cytisine has a considerable side effect profile. Potential side effects include appetite and weight changes, dizziness, psychiatric changes, sleep disturbance headaches, fatigue/lethargy, heart rate changes, hypertension, dyspnoea, diarrhea, nausea, heartburn, constipation, vomiting, abdominal pain, rash and myalgia.
- Quality data on serious adverse events associated with cytisine use is limited; known examples include stroke, heart attack, cancer and serious mental illness.
- There is insufficient data to determine safe use of cytisine in children and individuals who are pregnant or breastfeeding and use of cytisine in these population may lead to harm.

Benefits:

- Cytisine is used to reduce nicotine cravings in smokers who are willing to stop smoking and assists with smoking cessation.
- Cytisine may lead to an increase in the likelihood of smoking cessation or minimisation.

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

- Cytisine is used as a smoking cessation aid.

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

c) the toxicity of a substance

- Cytisine is generally well tolerated with some demonstrated toxicity at high doses.

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

- Cytisine is typically subject to a complex dosing regimen, which involves a decreasing dosage schedule.
- Various dosage forms are possible, including tablets and lozenges (oral troche).

e) the potential for abuse of a substance

- The potential for abuse of cytisine is reported as minimal.

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

- Cytisine is a new drug to the Australian market with limited local experience of use.
- The need to establish clinical guidelines for cytisine use and integration into existing smoking cessation guidelines may require consideration.
- Health professional advice may be needed to guide patients to access additional supports such as Quitline.

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

I have made an interim decision to create a Schedule 3 entry for cytisine for divided oral and oromucosal preparations with a maximum recommended daily dose of 9 mg as an aid in withdrawal from tobacco smoking in adults, and a Schedule 4 entry to capture all other preparations of cytisine.

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

Cytisine is a plant-derived oral smoking cessation aid that is used to reduce nicotine withdrawal symptoms. Cytisine has been available in Eastern and Central European countries for many years, and it has become available in Canada, UK and Ireland recently. Cytisine is a partial nicotine receptor agonist and belongs to the same class of medicine as varenicline, a Schedule 4 (prescription only) medicine that is indicated for smoking cessation (s 52E (1)(b) of the Act). There is no significant difference in abstinence rates between cytisine and varenicline and it is likely that the two substances have similar adverse effects profile.

With respect to s 52E (1)(a) and (c) of the Act, I have considered the evidence provided by the applicant in support of the safety and efficacy of cytisine. I agree with the Committee that cytisine has been shown to be more effective than placebo and nicotine replacement therapy (NRT) as a smoking cessation aid. However, cytisine use is associated with more adverse events than other NRTs. I note one of the clinical studies reported up to 16% of participants ceased taking cytisine due to adverse effects.[4]

The Application states that cytisine may interact with some commonly used medicines such as streptomycin, theophylline, clozapine, ropinirole, and hormonal contraceptive pills, and reduce their effectiveness. There is limited clinical experience for cytisine use in individuals with liver or kidney impairment; as such cytisine may not be suitable for these patient groups. Individuals who have unstable angina, recent heart attack, clinically significant cardiac arrhythmias (irregular heart rhythm) and stroke are also not recommended to take cytisine. I recognise the common adverse effects of cytisine are generally limited to gastrointestinal side effects, dry mouth, dizziness, and increased

[4] Ofori, S., Lu, C., Olasupo, O.O., Dennis, B.B., Fairbairn, N., Devereaux, P.J. and Mbuagbaw, L., 2023. Cytisine for smoking cessation: a systematic review and meta-analysis. Drug and Alcohol Dependence, p.110936.

appetite, and some of these adverse events may be attributable to nicotine withdrawal rather than the use of cytisine.

Overall, I agree with the concerns expressed by the Committee and in the Submissions surrounding the lack of quality data on serious adverse events with cytisine use. There is also insufficient data to determine the safe use of cytisine in children and individuals who are pregnant or breastfeeding.

Turning my mind to s 52E (1)(d) and (f) of the Act, I agree with the Committee that behavioural support along with pharmacotherapy is critical for successful smoking cessation and attempts to quit smoking without assistance have a relatively low success rate. Many NRT preparations, such as nicotine gums and patches, available for general sale from supermarkets and convenience stores have a long history of use in Australia. They are included in existing smoking cessation guidelines in Australia and there are various tools and resources to adequately support the consumers.

I recognise there is limited local experience of cytisine use. Currently there are no cytisine products included on the Australian Register of Therapeutic Goods (the Register), and cytisine is not included in existing smoking cessation guidelines in Australia. The potential interactions with other medicines and lack of local experience in align with scheduling factors 6 and 8 for Schedule 4 substances. However, smoking habit can be easily identified by the consumer (factor 1 for Schedule 3) and diagnosis management or monitoring the habit does not require medical practitioner intervention (factor 1 for Schedule 4). I noted that the common adverse effects of cytisine use are non-serious, and I am satisfied that for the proposed indicated usages of cytisine, pharmacist oversight can sufficiently mitigate these risks (factors 1 and 3 for Schedule 3 substances). Pharmacists can also provide adequate support and guidance for the consumer. Further, cytisine preparations require a relatively complex dosage regimen which may pose risks of dosing error, supporting the case for health professional intervention in the use of cytisine. I consider a Schedule 3 classification for cytisine will enable greater accessibility to consumers trying to quit smoking and will provide additional public health benefits.

Because of the lack of history of use in Australia, limited data on adverse events to determine safe usage and absence of guidance and support for users, I am of the view that a Schedule 2 classification is not appropriate for cytisine.

Regarding the specifics for the Schedule 3 entry for cytisine, I consider that it should be limited to use patterns based on the available evidence. I note that current evidence only supports the safe use of cytisine in adults and, although there is no consensus on the optimal dosing regimen and duration of cytisine treatment, existing data supports a maximum daily dose of 9 mg of cytisine.

I note, under s 52E (1)(d) of the Act, while the proposed cytisine product outlined in the application is in tablet form, there are reports of unregistered cytisine lozenges already available to consumers in Australia. Therefore, I have decided to include oral and oromucosal preparations of cytisine in Schedule 3 when used for smoking cessation in adults with a maximum recommended daily dose of 9 mg. I note the inclusion of these preparations in the Schedule 3 entry will require a sponsor to submit an application to the TGA with sufficient evidence to support such use.

Due to the unknown risks associated with usages of cytisine that are currently not supported by evidence, such as nicotine vaping cessation or use in younger individuals, I am of the view these usages should be initiated and supervised by medical practitioners. Therefore, I have decided to include cytisine of other preparations or indicated for other uses in Schedule 4.

I have considered the Committee's recommendation to include 'nicotine dependence' as an indication in the Schedule 3 entry. I acknowledge that there is an increasing popularity of non-smoking nicotine products and there is a need for aids to manage nicotine withdrawal associated with non-smoking nicotine products in the community. However, despite some emerging evidence supporting cytisine use in nicotine vaping cessation,[5] at present most evidence supporting the use of cytisine is for smoking cessation.

[5] Rigotti, N.A., Benowitz, N.L., Prochaska, J.J., Cain, D.F., Ball, J., Clarke, A., Blumenstein, B.A. and Jacobs, C., 2024. Cytisinicline for Vaping Cessation in Adults Using Nicotine E-Cigarettes: The ORCA-V1 Randomized Clinical Trial. JAMA Internal Medicine.

I have considered the matters set out in the Guidelines for advertisements for medicines containing Schedule 3 substances to determine whether cytisine is suitable for advertising. Considering the lack of local experience in cytisine use, insufficient evidence to support the safe use of cytisine in certain patient groups, and potential risks of interactions with other medicines, I agree with the Committee that cytisine is not suitable for advertising until more local data and evidence on cytisine use is available.

After considering the information provided in the application, the public submissions, Committee's advice and the SPF factors, I have made an interim decision to create new Schedule 3 and 4 entries for cytisine as outlined above, with an implementation date of 1 October 2024 to avoid any unnecessary delay to industry.

Implementation date

1 October 2024

Interim decision in relation to dextromethorphan

Proposal

The Delegate proposed to amend the current Schedule 2 entry for dextromethorphan to Schedule 3. Under the proposal, preparations containing 600 mg or less of dextromethorphan with a recommended daily dose of 120 mg or less, will only be available after consultation with a pharmacist. All other preparations of dextromethorphan will remain in Schedule 4 (prescription-only).

Interim decision

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

Materials considered

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

- The proposal to amend the current Poisons Standard with respect to dextromethorphan (the Proposal)
- The 14 public submissions, received in response to the pre-meeting public consultation (the Submissions)
- The advice received from the 44th meeting of the Advisory Committee on Medicines Scheduling (the Committee)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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 2012 WHO Expert Committee on Drug Dependence
- The SPF, and
- The Handbook.

Summary of Committee advice to the Delegate

The Committee did not recommend any changes to the scheduling of dextromethorphan in the current Poisons Standard as there was insufficient Australian data to support the proposed changes. However, the Committee recommended examination of existing data on dextromethorphan misuse and abuse from a wider range of sources and collection of additional new data, if required, with a view to reconsider its scheduling.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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:

- When exceeding approved dosages, dextromethorphan can act as a dissociative hallucinogen.

Benefits:

- Dextromethorphan is an antitussive agent used in the treatment of dry cough with relatively limited evidence of efficacy, but a historically well-established toxicity and safety profile.
- Dextromethorphan is well tolerated when used at recommended doses.

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

- Dextromethorphan is commonly used in the treatment of dry cough and is widely used.

c) the toxicity of a substance

- Dextromethorphan is well tolerated at recommended doses, although there is potential for serotonin syndrome when combined with other serotonergic agents.
- Symptoms in overdose include tachycardia, changes in blood pressure, hyperexcitability, somnolence, elevated body temperature, drowsiness, and seizures.
- Dextromethorphan is the d-isomer of the codeine analogue methorphan but does not act through opioid receptors. It affects serotonin, norepinephrine, NMDA, and sigma-1 receptors in the brain.

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

- Dextromethorphan is typically presented in oral liquids, pastilles, tablets and capsules as either a single ingredient or co-formulated with other active ingredients in the management of cold and flu symptoms.
- Schedule 2 preparations of dextromethorphan are supplied in a pack containing 600 mg or less of dextromethorphan and with a recommended daily dose of 120 mg or less.

e) the potential for abuse of a substance

- When consumed at supratherapeutic doses dextromethorphan produces dissociative effects and is subject to abuse.

- A report from the WHO Expert Committee on Drug Dependence in 2012 concluded that "...the abuse potential of dextromethorphan is relatively low, intoxications are rare, and reports of dependence are infrequent."
- There is limited evidence of widespread abuse in Australia.

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

- The removal of pholcodine-containing medicines from the Australian market means that the only treatments available without a prescription for dry cough are dihydrocodeine and dextromethorphan.
- In the absence of any Schedule 2 options for cough suppression, consumers may self-select an inappropriate cough preparation such as an expectorant or mucolytic, which would be ineffective.
- Greater level of pharmacovigilance activity by the TGA may be required.
- That there should be a review of existing data concerning the misuse and abuse of dextromethorphan.
- The increase in regulatory burden is not justified at this time.

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

I have made an interim decision not to amend the Poisons Standard with regards to dextromethorphan. In making this decision, I agree with the Committee's findings on the relevant provisions of section 52E of the Act. Whilst I remain of the view that dextromethorphan poses a risk of misuse or abuse as evidenced by international reports, further examination of the evidence of misuse and abuse in Australia is required. I also note that despite a lack of substantive evidence of dextromethorphan's efficacy as an antitussive agent it has a history of relatively safe and well-tolerated usage in the treatment of dry cough.

I have considered the 14 public submissions received during the pre-meeting consultation period. Seven submissions supported the proposal, 2 supported it partially and 5 opposed.

Interested parties were given the choice to select from options to indicate their support or opposition to the proposed amendment without providing a written component. Three of the supportive submissions provided written responses. These submitters highlighted the increasing numbers of dextromethorphan misuse and hospitalisations reported to the New South Wales Poisons Information Centre (NSWPIC) in recent years. They also noted that dextromethorphan abuse has been reported in adults and adolescents due to its ketamine-like side effects when ingested in high doses. Further, studies have shown that in international jurisdictions dextromethorphan abuse is significantly reduced with additional controls on the sale of dextromethorphan such as monitoring and recording of supply, patient education and prohibiting the supply of bulk quantities.

Two written submissions partially supporting the proposal noted the lack of over-the-counter options to treat dry cough since the removal of pholcodine from the Australian market. These submissions argued significant data is required to understand the extent of misuse of cough suppressants in Australia. Submitters recommended that additional access restrictions, such as the creation of an Appendix M entry requiring prescription monitoring would reduce risks of dextromethorphan misuse. These submissions also noted the conflicting evidence on dextromethorphan's efficacy as an antitussive agent.

Four written submissions opposing the proposal highlighted the importance of people's access to over-the-counter treatment options for dry cough. These submissions emphasised the lack of evidence of the extent of dextromethorphan misuse in Australia. They noted that dextromethorphan has been available over-the-counter since 1998 in Australia and for over 50 years globally, and has been shown to be well-tolerated and safe at the recommended dosage. Submitters commented that

reports in the Database of Adverse Event Notifications (DAEN) do not support that the frequency of dextromethorphan misuse or abuse has increased. Submitters also referred to a report by the World Health Organization (WHO) Expert Committee on Drug Dependence[6] that concluded that 'the abuse potential of dextromethorphan is relatively low, intoxications are rare, and reports of dependence are infrequent.' Further, there is no evidence that up-scheduling of dihydrocodeine (see below) would increase the frequency of dextromethorphan misuse, and amending the scheduling of dextromethorphan based on any potential increase in misuse is premature and unprecedented.

Turning my mind to s 52E(1)(a) and (b) of the Act, I have considered the use of dextromethorphan as an antitussive agent. Whilst there is a long history of non-prescription usage of dextromethorphan, I note the lack of substantive evidence of dextromethorphan efficacy in the treatment of dry cough.

With regards to s 52E(1)(c) of the Act, I note that dextromethorphan is well tolerated and has a well-established safety profile when consumed at recommended doses. However, I agree with the Committee that dextromethorphan poses a risk of serotonin syndrome when combined with other serotonergic agents. I note that the symptoms of dextromethorphan overdose include tachycardia, changes in blood pressure, hyperexcitability, somnolence, elevated body temperature, drowsiness, and seizures.

Regarding s 52E(1)(d) of the Act, dextromethorphan is typically presented in oral liquids, pastilles, tablets and capsules as either a single ingredient for the treatment of dry cough, or co-formulated with other active ingredients in preparations for the management of cold and flu symptoms. Schedule 2 preparations of dextromethorphan are supplied in a pack containing 600 mg or less of dextromethorphan and with a recommended daily dose of 120 mg or less.

Turning my mind to s 52E(1)(e) of the Act, I note that misuse of dextromethorphan occurs when consumed at supratherapeutic doses. Data provided by NSWPIC for dextromethorphan showed that callers on average ingested 600 mg dextromethorphan (equivalent to 200 mL of some common liquid preparations containing 15 mg per 5 mL dextromethorphan). The Committee discussed a recent analysis of drug abuse and dependence data in the WHO pharmacovigilance database VigiBase® that indicated a strong signal for dextromethorphan abuse. I note the Committee's views that:

- adverse events are likely under-reported as dextromethorphan is currently a Schedule 2 substance
- social media and cultural trends could drive unscrupulous consumer demand for dextromethorphan very rapidly
- inclusion in Schedule 3 would not significantly impact reputable use but could provide regulatory protection against misuse or abuse.

However, as noted by the Committee and public submissions, currently there is limited evidence of widespread misuse or abuse of dextromethorphan in Australia. I also note the conclusions of the 35th report of WHO Expert Committee on Drug Dependence discussed above.

With respect to s 52E(1)(f) of the Act, I recognise that at present there are limited options for non-prescription dry cough medicine. Following the withdrawal of pholcodine from the Australian market, dihydrocodeine and dextromethorphan are the only two dry cough medicines that can be accessed without a prescription. Removing the non-prescription availability to dextromethorphan may cause inconvenience to consumers in accessing dry cough medicines in a timely manner. I agree with the Committee that in the absence of any Schedule 2 options for cough suppression, consumers may self-select an inappropriate cough preparation such as an expectorant or mucolytic, which would be ineffective.

I have considered the information provided in the public submissions and the advice provided by the Committee which have presented the limited evidence of the extent of misuse or abuse of dextromethorphan in Australia. As well as considering the SPF factors, I am of the opinion that the up-scheduling of dextromethorphan to Schedule 3 is not justified at this time. Therefore, I have made an interim decision not to amend the scheduling of dextromethorphan in the Poisons Standard. Further

[6] Thirty-fifth Report of the Who Expert Committee on Drug Dependence, 2012

examination of all the available evidence of dextromethorphan abuse in Australia and collection of additional data, if required, will be undertaken for any reconsideration of the scheduling of dextromethorphan.

Interim decision in relation to dihydrocodeine

Proposal

The Delegate received an application to delete the current Schedule 3 entry for dihydrocodeine from the Poisons Standard. The proposal seeks to change cough suppression preparations containing dihydrocodeine that are currently available as Schedule 3 (Pharmacist Only) medicines to Schedule 4 (Prescription Only).

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to amend the scheduling of dihydrocodeine in the Poisons Standard as follows:[7]

Schedule 8

DIHYDROCODEINE except when included in Schedule 3 or 4.

Schedule 4

DIHYDROCODEINE when compounded with one or more other therapeutically active substances:

(a) in divided preparations containing not more than 100 mg of dihydrocodeine per dosage unit; or
(b) in undivided preparations with a concentration of not more than 2.5% of dihydrocodeine

except when included in Schedule 3.

Schedule 3 – Amend entry

DIHYDROCODEINE when:

(a) indicated for cough suppression; and

(b) compounded with one or more other therapeutically active substances; and~~:~~

~~in divided preparations containing 10 mg or less of dihydrocodeine per dosage unit and with a recommended dose not exceeding 15 mg of dihydrocodeine; or~~

(c) in undivided preparations containing 0.25% or less of dihydrocodeine with a recommended dose not exceeding 15 mg of dihydrocodeine; and

(d) in a primary pack containing not more than 100 mL.

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

Appendix K, Clause 1 – Human medicines required to be labelled with a sedation warning.

Item	Poison
45	DIHYDROCODEINE

Materials considered

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

- The application to amend the current Poisons Standard with respect to dihydrocodeine (the Application)
- The 12 public submissions received in response to the pre-meeting public consultation (the Submissions)
- The advice received from the 44th meeting of the Advisory Committee on Medicines Scheduling (the Committee)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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 SPF, and
- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that the scheduling of dihydrocodeine in the Poisons Standard be amended as follows:[8]

Schedule 8

DIHYDROCODEINE except when included in Schedule 3 or 4.

Schedule 4

DIHYDROCODEINE when compounded with one or more other therapeutically active substances:

(a) in divided preparations containing not more than 100 mg of dihydrocodeine per dosage unit; or

(b) in undivided preparations with a concentration of not more than 2.5% of dihydrocodeine

except when included in Schedule 3.

Schedule 3 – Amend entry

DIHYDROCODEINE when:

(a) indicated for cough suppression; and

(b) compounded with one or more other therapeutically active substances; and~~:~~

~~in divided preparations containing 10 mg or less of dihydrocodeine per dosage unit and with a recommended dose not exceeding 15 mg of dihydrocodeine; or~~

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

(c) ~~in undivided preparations containing 0.25% or less of dihydrocodeine with a recommended dose not exceeding 15 mg of dihydrocodeine~~; and

(d) in a primary pack containing not more than 100 mL.

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Appendix K, Clause 1 – Human medicines required to be labelled with a sedation warning.

Item	Poison
45	DIHYDROCODEINE

The Committee recommended an implementation date of **1 June 2025** to allow industry sufficient time to make necessary changes in response to the scheduling change.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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:

- Dihydrocodeine is an opioid derivative that poses a potential risk of dependence even at therapeutic doses.
- Overdose of dihydrocodeine is associated with somnolence and progression to unconsciousness, coma, miotic pupils, rhabdomyolysis, non-cardiac pulmonary oedema, bradycardia, hypotension, respiratory depression or apnoea, with severe cases resulting in fatality.

Benefits:

- Dihydrocodeine is an antitussive agent.

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

- Dihydrocodeine is indicated for relief of unproductive dry cough.

c) the toxicity of a substance

- Dihydrocodeine presents with a risk of respiratory depression by acting on the respiratory centre in the brain stem.
- Use of dihydrocodeine in combination with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, can result in sedation, respiratory depression, coma or even death.

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

- Dihydrocodeine is available without a prescription (Schedule 3) as an oral liquid product in 100 mL and 200 mL pack sizes for the relief of stubborn unproductive dry cough.
- The current formulation of the oral liquid (Rikodeine®) contains sorbitol which is intended to limit potential misuse by exerting unwanted gastrointestinal side effects when the daily dose is exceeded.

e) the potential for abuse of a substance

- The risk of addiction may be increased in people with personal or family history of substance misuse (including alcohol and prescription and illicit drugs) or mental health problems.
- Long-term use of dihydrocodeine presents a significant risk of tolerance development, physical dependence and withdrawal.
- The substance can produce euphoria and has known potential for abuse.

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

- Dihydrocodeine guidelines and regulations in Australia are inconsistent with other similar jurisdictions including the US FDA, European Commission, New Zealand Medsafe, Health Canada and Ireland. The proposal to delete the Schedule 3 entry would bring Australia in line with other regulators.
- Up scheduling of dihydrocodeine may result in diversion to other cough suppressants such as dextromethorphan that are currently available in pharmacies.
- Recommend examination of existing data from a wider range of sources, with collection of additional new data, if required, with a view to reconsider the scheduling of dihydrocodeine in 12 months.
- Additional monitoring measures at point of sale may be considered to support appropriate supply of dihydrocodeine.
- Sorbitol content and its deterrent effect to dihydrocodeine misuse should be examined by the TGA.

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

I have made an interim decision to amend the Schedule 3 entry for dihydrocodeine to remove the reference to divided preparations and to place a volume restriction on undivided preparations. The detailed reasons for my decision follow.

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

I have considered the 12 public submissions received during the pre-meeting consultation period. Eight of them were supportive of the proposal while 4 opposed it.

Interested parties were given the choice to indicate their support or opposition to the proposed amendments with or without providing a written component. Two of the supportive submissions provided written responses highlighting dihydrocodeine’s potential for misuse and abuse and lack of measures to prevent consumers from visiting multiple pharmacies to request this medicine.

Four submissions opposed the proposal and provided written components stating dihydrocodeine has a long history of use and the safety profile is well known. These submissions argued that the lack of substantive evidence to show the extent of misuse or abuse of dihydrocodeine in Australia does not

support the proposal. Further, the up-scheduling of dihydrocodeine will impose barrier to consumers accessing dry cough medicine due to limited treatment options at present.

In relation to s 52E(1)(a), (c) and (e) of the Act, dihydrocodeine is an opioid derivative that falls into the same class of medicine with codeine and morphine and has known potential for abuse, misuse and addiction. I note that a dose of 100 mg dihydrocodeine is equivalent to approximately 10 mg of oral morphine.[9] The use of dihydrocodeine is associated with high-risk adverse events such as respiratory depression and sedation. Further, repeated use of dihydrocodeine is associated with risks for developing tolerance, physical dependence and withdrawal. These risks are further increased in individuals with a personal or family history of mental health problems or substance misuse. Dihydrocodeine is contraindicated in individuals with respiratory failure, asthma or chronic obstructive pulmonary disease (COPD). Concurrent use with other substances such as benzodiazepines or central nervous system depressants, including alcohol, increases the risks of sedation, respiratory depression, coma, or death. Taking these matters into consideration, I consider dihydrocodeine aligns with some of the scheduling factors of Schedule 4.

Regarding s 52E(1)(b) and (d) of the Act, currently there is only one dihydrocodeine containing product listed on the Australian Register of Therapeutic Goods (the Register). The product is an oral liquid formulation indicated for the suppression of dry cough and available in 100 mL and 200 mL pack sizes as a Schedule 3 (pharmacist only) medicine. I note the proposal aims to restrict the access to this dihydrocodeine preparation to Schedule 4 (prescription only). The current formulation of this product contains sorbitol which is intended to limit potential misuse of the preparation by exerting unwanted gastrointestinal side effects if the daily dose is exceeded.

Concerning other matters relevant to public health (s 52E(1)(f) of the Act), I note dihydrocodeine regulations in Australia are inconsistent with other similar jurisdictions including the United States, New Zealand, Canada and Ireland, which categorise dihydrocodeine as a prescription medicine. Removing non-prescription availability of dihydrocodeine will reduce public health risks in relation to dihydrocodeine and bring Australia's regulation on dihydrocodeine more in line with international jurisdictions.

I acknowledge the long-standing concerns in the community surrounding dihydrocodeine misuse. However, I am mindful of the Committee advice that at present there is limited Australian data to demonstrate widespread misuse of dihydrocodeine to support the deletion of the Schedule 3 entry. I note that there is evidence of increasing dihydrocodeine misuse and overdose deaths in the UK.[10] However, in the UK dihydrocodeine is commonly used for pain relief and at much higher doses and, as such, this medicine is generally supplied to a higher risk population. I agree with the Committee that it may not be appropriate to draw on this data to support scheduling changes in Australia.

I also recognise that at present there are limited options for non-prescription medicine for dry cough. Following the withdrawal of pholcodine from the Australian market, dihydrocodeine and dextromethorphan are the only two dry cough medicines that can be accessed without a prescription. Further, dextromethorphan may not be suitable to some consumers due to its potential for drug-drug interactions, making dihydrocodeine a safer option for these consumers. Therefore, removing the non-prescription availability to dihydrocodeine preparation may cause inconvenience to consumers in accessing dry cough medicines in a timely manner.

In balancing the potential misuse, abuse and addiction potential of dihydrocodeine as an opioid derivative and the inconvenience of general pubic in accessing dry cough medication, I have decided to amend the Schedule 3 entry for dihydrocodeine to place a volume restriction of 100 mL in relation to undivided preparations. A 100 mL bottle of the Schedule 3 dihydrocodeine product provides 2-5 days of treatment when taken at the recommended adult dose, which is sufficient for the relief of short-term dry cough. I am of the opinion that this decision will continue to enable consumers to access dry cough medicine in a timely manner and then encourage consumers to seek medical advice when this medicine is required for a longer period.

[9] Dose equivalents and changing opioids

[10] Rock, K.L., Reynolds, L.M., Rees, P. and Copeland, C.S., 2022. Highlighting the hidden dangers of a 'weak' opioid: Deaths following use of dihydrocodeine in England (2001–2020). *Drug and alcohol dependence*, *233*, p.109376.

I have also decided to remove the reference to divided preparation from the Schedule 3 entry for dihydrocodeine as dihydrocodeine aligns with some of the scheduling factors of Schedule 4. Unlike the undivided preparation, there is no safety data on the divided preparation to support to safe use of this preparation as a Schedule 3 medicine. I find there is insufficient basis to retain the inclusion of divided preparations of dihydrocodeine in the Schedule 3 entry considering the potential of abuse, misuse, and addiction potential of this substance. I note at present there are no divided dihydrocodeine preparations included in the Register. As such, this decision will cause minimal inconvenience to consumers.

I have considered a suggestion in one public submission to create a new Appendix M entry for dihydrocodeine to require record keeping of dihydrocodeine supply using Real Time Prescription Monitoring (RTPM). I acknowledge that such a measure would better assist pharmacists to supply dihydrocodeine appropriately and set barriers to accessing large quantities of dihydrocodeine from multiple pharmacies. It will also enable greater pharmacovigilance activity and enable data collection to better understand dihydrocodeine use and misuse. However, the implementation of the Poisons Standard is given effect through relevant state and territory legislations and implementation of such measure requires agreement from state and territory governments, especially as the RTPM system is only implemented for medicine requiring a prescription (Schedules 4 and 8). At this stage, I am of the view that further discussion and detailed consideration with state and territory governments are required to establish this mechanism.

I am of the view that while a potential for the misuse, abuse or addiction exists for dihydrocodeine, currently there is not enough evidence to support the deletion of the Schedule 3 entry for dihydrocodeine. I agree with the Committee that further review of existing data on the dihydrocodeine misuse is required. Collection of additional data may also be required and I reserve the right to reconsider the scheduling of dihydrocodeine in future should relevant new information become available. I have decided on an implementation date of 1 October 2025 to allow industry sufficient time to implement the packaging changes in response to the decision.

Implementation date

1 October 2025

Interim decision in relation to ethylmorphine

Proposal

The Department of Health and Aged Care proposed deletion of the Schedule 2 entry for ethylmorphine. This will effectively classify all preparations containing ethylmorphine as prescription-only medicines.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to amend the scheduling of ethylmorphine in the Poisons Standard as follows:[11]

Schedule 8 – Amend Entry

ETHYLMORPHINE **except** when included in Schedule ~~2 or~~ 4.

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

Schedule 4 – Amend Entry

ETHYLMORPHINE when compounded with one or more other therapeutically active substances:

(a) in divided preparations containing not more than 100 mg of ethylmorphine per dosage unit; or

(b) in undivided preparations with a concentration of not more than 2.5% of ethylmorphine~~;~~.

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

Schedule 2 – Delete Entry

~~ETHYLMORPHINE when:~~

(a) compounded with one or more other therapeutically active substances:

~~(i) in divided preparations containing 10 mg or less of ethylmorphine per dosage unit; or~~

~~(ii) in undivided preparations containing 0.25% or less of ethylmorphine; and~~

(b) labelled with a recommended dose not exceeding 15 mg of ethylmorphine.

Index – Amend Entry

ETHYLMORPHINE

Schedule 8
Schedule 4
~~Schedule 2~~

Materials considered

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

- The proposal to amend the current Poisons Standard with respect to ethylmorphine (the Proposal)
- The 10 public submissions received in response to the pre-meeting public consultation (the Submissions)
- The advice received from the 44th meeting of the Advisory Committee on Medicines Scheduling (the Committee)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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 United Nations Single Convention on Narcotic Drugs 1961 (the Single Convention)
- The SPF, and
- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended that the scheduling of ethylmorphine in the Poisons Standard be amended as follows[12]:

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

Schedule 8 – Amend Entry

ETHYLMORPHINE **except** when included in Schedule ~~2 or~~ 4.

Schedule 4 – Amend Entry

ETHYLMORPHINE when compounded with one or more other therapeutically active substances:

(a) in divided preparations containing not more than 100 mg of ethylmorphine per dosage unit; or

(b) in undivided preparations with a concentration of not more than 2.5% of ethylmorphine~~;~~.

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

Schedule 2 – Delete Entry

~~ETHYLMORPHINE when:~~

~~(a) compounded with one or more other therapeutically active substances:~~

~~(i) in divided preparations containing 10 mg or less of ethylmorphine per dosage unit; or~~

~~(ii) in undivided preparations containing 0.25% or less of ethylmorphine; and~~

~~(b) labelled with a recommended dose not exceeding 15 mg of ethylmorphine.~~

Index – Amend Entry

ETHYLMORPHINE

Schedule 8
Schedule 4
~~Schedule 2~~

The Committee recommended an implementation date of **1 October 2024**, as there are no registered products that would be affected by the change.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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:

- Ethylmorphine is metabolised to morphine and, therefore, has a potential for abuse.
- There is a lack of reliable information regarding the toxicity, real-world use and respiratory depression symptoms associated with ethyl morphine use.

Benefits:

- Ethylmorphine is a potential antitussive agent for the treatment of dry coughs.

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

- Current use of ethylmorphine is limited as there are no commercially available products in Australia. However, given its mechanism of action as an antitussive agent and shifts

in the availability of antitussives in recent years, there is a possibility of increased use in the future.

c) the toxicity of a substance

– There is no reliable toxicity or safety data available for ethylmorphine, however, there are potential respiratory depression and dependency concerns due to its metabolism to morphine.

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

– There are no marketed products in Australia.

e) the potential for abuse of a substance

– Ethylmorphine is metabolised to morphine and may be associated with the potential for abuse and poisoning.

– Opioid with dependence liability.

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

– Nil.

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

Ethylmorphine is a legacy entry and has not been considered since the early 1990s. I have decided to consider the scheduling of ethylmorphine concurrently with dextromethorphan and dihydrocodeine to review whether current access remains appropriate. I have made an interim decision to delete the Schedule 2 entry for ethylmorphine to make all preparations containing ethylmorphine prescription-only medicines.

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

I have considered the 10 public submissions received during the pre-meeting consultation period. Six submissions supported the proposal, 2 supported it partially and 2 opposed.

Interested parties were given the choice to indicate their support or opposition to the proposed amendment without providing a written component. Three written submissions received in support stated that opioids should not be available to patients without assessment by a pharmacist or doctor would welcome any measures that decreased the potential of opioid abuse or misuse. The written submissions that expressed partial support were of the view that mandatory recording of the supply of Schedule 3 ethylmorphine preparations using Real Time Prescription Monitoring (RTPM) could satisfactorily reduce the risks.

In relation to s 52E(b) of the Act, ethylmorphine is an opioid that has been used as an antitussive agent and an analgesic. There are currently no registered over-the-counter (OTC) products containing ethylmorphine on the Australian Register of Therapeutic Goods (the Register). However, ethylmorphine preparations can be imported or compounded without a prescription or consultation with a health practitioner. Through research and consultations with the Committee and the public, I did not find or receive any information to suggest supply of unregistered ethylmorphine products in Australia. Therefore, the level of use of ethylmorphine in Australia is expected to be minimal.

In considering s 52E(1)(a) and (c) of the Act, there are limited safety and toxicity data on ethylmorphine. Structurally, it is the 3-ethoxy congener of morphine and is partially metabolised into two active metabolites, morphine and morphine-6-glucuronide.[13] The data on ethylmorphine

[13] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1365072/pdf/brjclinpharm00008-0026.pdf

metabolism are limited. One study involving 10 participants indicated a high variation in ethylmorphine conversion to morphine. However, up to 15% of the ethylmorphine dose was converted to morphine suggesting a potential for abuse. Further, the limited information available on ethylmorphine use under normal conditions aligns with Schedule 4, factor 8 of the SPF.

I am also concerned about the acute risks associated with ethylmorphine, such as respiratory depression. I note respiratory depression can be compounded by many other drugs commonly used in Australia. For example, prescription opioid products include a warning in the product information (PI) regarding use of opioids with benzodiazepines, gabapentinoids, antihistamines, tricyclic antidepressants, antipsychotics, cannabis or other central nervous system (CNS) depressants, including alcohol possibly resulting in profound sedation, respiratory depression, coma, and death.[14] Consistent with Schedule 4, factor 6 of the SPF, I consider such potentially serious interactions require supervision by a medical practitioner.

Considering the limited safety data and several known and unknown risks associated with ethylmorphine, I am of the opinion that the risks outweigh the benefits for the use of OTC ethylmorphine preparations. I acknowledge a public submission proposing the use of Appendix M and RTPM but am not convinced that such a mechanism is adequate to manage the risks. Further, implementation of such restrictions are matters for the jurisdictions and require further discussion as noted above. I have, therefore, decided to delete the Schedule 2 entry for ethylmorphine, making it available only as a prescription-only medicine. Since there are currently no ethylmorphine products on the Register, the impact will be negligible.

Regarding the Schedule 4 and 8 entries of ethylmorphine, I note ethylmorphine is included in Schedule II of the United Nations Single Convention on Narcotic Drugs 1961, which aligns with Schedule 8, Factor 1 of the SPF and is consistent with the current Schedule 8 entry for ethylmorphine. Ethylmorphine when compounded with one or more other ingredients and containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more than 2.5 per cent in undivided preparations is listed in Schedule III of the Convention and aligns with the current Schedule 4 entry in the current Poisons Standard. I am of the view the parent entry for ethylmorphine in Schedule 8 and the concentration and dosage limits in the Schedule 4 entry remain appropriate.

Implementation date

1 October 2024

[14] https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2010-PI-05156-3

Interim decisions on proposed amendments referred to the Advisory Committee on Chemicals Scheduling (ACCS #38, March 2024)

Interim decision in relation to ethyl lactyl retinoate

Proposal

The Delegate received an application to amend the Schedule 4 entry for tretinoin to exempt dermal cosmetic preparations that contain ethyl lactyl retinoate. Under the current scheduling, ethyl lactyl retinoate may be interpreted as a derivative of tretinoin and, therefore, subject to the controls imposed on Schedule 4 substances, such as the requirement for a valid prescription.

Interim decision

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

Materials considered

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

- The application to amend the current Poisons Standard with respect to ethyl lactyl retinoate (the Application)
- The 9 public submissions, received in response to the pre-meeting public consultation (the Submissions)
- The advice received from the 38th meeting of the Advisory Committee on Chemicals Scheduling (the Committee)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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 SPF, and
- The Handbook.

Summary of Committee advice to the Delegate

The Committee recommended, pending review by the Delegate of any additional toxicity data that may be available on ethyl lactyl retinoate, that the Schedule 4 entry for tretinoin in the current Poisons Standard be amended as follows:[15]

Schedule 4 – Amend entry

TRETINOIN **except**:

a) the ester hydroxypinacolone retinoate in preparations for dermal use containing 0.5% or less of hydroxypinacolone retinoate; or

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

b) ethyl lactyl retinoate in preparations for dermal use containing 0.1% or less of ethyl lactyl retinoate.

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TRETINOIN

Schedule 4
Appendix D, clause 4
Appendix F, clause 4
Appendix L, clause 2

The Committee recommended no changes to the entries for tretinoin in Appendix D, F or L.

The Committee recommended an implementation date of **1 October 2024**, as there was no reason to delay the implementation of the decision. However, the Committee recommended the Delegate reviews any additional toxicity data, particularly from international assessments, that may be available prior to making a decision.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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

Risks:

- Evidence is limited on the teratogenic potential of ethyl lactyl retinoate.

Benefits:

- Ethyl lactyl retinoate is claimed to be a skin conditioner, however, it also has no known therapeutic applications.

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

- Dermal formulations and cosmetic preparations containing ethyl lactyl retinoate up to a concentration of 0.1%.

c) the toxicity of a substance

- *In vivo* conversion of ethyl lactyl retinoate to retinoic acid is plausible. The proposed two-step conversion process is slow and may release retinoic acid gradually.
- Ethyl lactyl retinoate is not readily absorbed in skin and has a low potential for causing harm via the dermal route as it is non-corrosive.
- There is demonstrated skin tolerance of dermal product preparations containing ethyl lactyl retinoate up to 0.1% concentration.
- The concentration cut-off of 0.1% is based on concentrations in cosmetic preparations such as serums and cleansers.
- Ethyl lactyl retinoate has the closest activity profile to retinol but is ten times less irritating than retinol.

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

- The proposed use of ethyl lactyl retinoate is in dermal preparations such as serums, oils and creams containing up to 0.1% ethyl lactyl retinoate.

e) the potential for abuse of a substance

– Nil.

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

– Ethyl lactyl retinoate is not regulated internationally and is used at low concentrations in cosmetic formulations in Europe, North American and New Zealand.

– The limited information available on the toxicity of the substance does not equate to safety. Further data including risk assessments conducted in other jurisdictions should be sought for a more informed assessment of the potential hazards associated with the cosmetic use of ethyl lactyl retinoate.

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

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

Ethyl lactyl retinoate (ELR) is an ester of retinoic acid. Tretinoin, the all-*trans* isomer of retinoic acid, is used as an active pharmaceutical ingredient in oral and dermal dosage forms and is included in the Poisons Standard as a Schedule 4 substance. Additional requirements under Appendices D, F and L also apply. The Poisons Standard provides that all derivatives of a substance, such as esters, are scheduled in the same way as the substance. Therefore, ELR is currently considered a Schedule 4 (Prescription Only) medicine. The Application seeks to allow use of the substance in dermal preparations by creating a new exemption in the Schedule 4 entry for tretinoin. Under the proposal, dermal preparations containing 0.1% or less of ELR would be exempt from scheduling and, therefore, permitted for use in products such as cosmetics.

Dermally applied tretinoin is effective for the treatment of acne but carries the health risks typical of retinoids. The risks range from local effects on the skin such as redness and peeling, through to significant systemic effects including teratogenicity. Therefore, tretinoin is contraindicated in pregnancy and dermal application of tretinoin is included in the TGA’s Prescribing Medicines in Pregnancy database under category D as a drug which “may be expected to cause an increased incidence of human foetal malformations or irreversible damage”. The Appendix F entry for tretinoin in the current Poisons Standard requires that all topical preparations containing tretinoin carry warning statements about possible birth defects and not to use during pregnancy. Under Appendix D of the current Poisons Standard, tretinoin for oral use is only available from or on the order of a specialist physician. Additional waring statements for oral usage required under Appendix F aim to ensure that the patient is not pregnant when starting treatment with tretinoin and remains so until at least one month after ceasing treatment.

I have considered the 9 public submissions received during the pre-meeting consultation period, of which 6 were supportive of the proposal, one partially supportive while two opposed.

Interested parties were given the choice to select from options to indicate their support or opposition to the proposed amendment without providing a written component. Three submissions in support of the proposal provided a written component. One of these proposed that the amendment should extend to all salts and derivatives of tretinoin for topical use due to their relatively low safety risk. However, given the uncertainty in the potency and dermal absorption of different tretinoin derivatives, and the potential harms to human health, I have decided not to extend an exemption to these salts and derivatives at this time.

There was one submission opposing the scheduling proposal for ELR with a written component. This submission drew a comparison with the scheduling of previously considered tretinoin derivative hydroxypinacolone retinoate (HPR). Dermal preparations containing 0.5% or less of HPR were

exempted from scheduling in January 2023,[16] on the basis of established safe use of the substance and evidence indicating that HPR is not metabolised *in vivo* to trans-retinoic acid (tretinoin). This opposing submission highlighted that the information included in the Application was insufficient to establish a safe use of ELR in topical preparations and in particular lacked data on teratogenicity.

With reference to s 52E(1)(a) and (b), I have considered the information presented in the Application and public submissions regarding the benefits and risks of the dermal use of ELR. I note the applicant's focus on the cosmetic use of ELR to improve skin appearance. The applicant claimed that ELR has been developed to minimise the side effects such as redness, peeling and general irritation of the skin typical with other topical retinoids. Further, the size of the ELR molecule is purported to sterically hinders its binding to the retinoid receptors.

With reference to s 52E(1)(c), the key issue regarding the toxicity of ELR is the potential for *in vivo* conversion of ELR to the known teratogen all *trans*-retinoic acid. This is especially pertinent if the substance is used in cosmetics during or while planning for pregnancy. The applicant provided data on an *ex vivo* skin absorption study. However, there are some methodological deficiencies in the study that do not quantify how much ELR was or was not metabolised to retinol, retinal or retinoic acid.

While the data provided by the applicant from Human Repeat Insult Patch Tests (HPIRT) indicated that ELR induced less skin irritation, the *in vitro* retinoid receptor gene expression analysis in pooled adult human keratinocyte cultures was less convincing. In the latter study, the relative expression of 6 retinoid genes (RAR alpha, beta and gamma; RXR alpha, beta and gamma) were somewhat reduced in the presence of ELR (0.250 µM) compared with retinal (0.175 µM) and retinol (3.490 µM), but not completely. Moreover, as the assay was not designed to qualify the downstream retinoid protein synthesis within these cell cultures, the effect on biological activity remains unknown.

With regards to s 52E(1)(f), I have noted the overseas use of ELR in cosmetics in Europe, North America and New Zealand where it is not regulated when used at low concentrations in cosmetic formulations. The ready availability of cosmetics containing ELR in these markets is not an indication of safety. While there is a lack of reported adverse events associated with ELR, self-reporting of adverse events from cosmetics use is expected to be lower than medicines which are common behaviours in the presence of mild-to-moderate reactions, as in the case of cosmetics.

Overall, while I note the improved skin tolerance for ELR and the proposed cut-off level of 0.1% based on typical concentrations in preparations available overseas, I remain unconvinced by the experimental data supplied to demonstrate that ELR is not hydrolysed into retinoic acid. Further, I am concerned by the lack of teratogenicity data and information establishing a history of safe use particularly in pregnant women. Therefore, I have decided not to amend the entry for tretinoin to exempt ELR.

[16] https://www.tga.gov.au/sites/default/files/2023-01/notice-of-final-decision-to-amend-or-not-amend-the-current-poisons-standard-acms-38-joint-acms-accs-31-accs-34.pdf

Interim decision in relation to niclosamide

Proposal

The Delegate received an application create a Schedule 5 entry for niclosamide when in tablet or paste preparations for companion animals, and a Schedule 6 entry for niclosamide except when included in Schedule 2 or 5.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, the Delegate has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in regard to niclosamide as follows:[17]

Schedule 6 – New entry

NICLOSAMIDE **except** when included in Schedule 2 or 5.

Schedule 5 – New entry

NICLOSAMIDE in tablet or paste preparations for use in companion animals.

Schedule 2

NICLOSAMIDE for human therapeutic use.

Index – Amend entry

NICLOSAMIDE

Schedule 6
Schedule 5
Schedule 2

Materials considered

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

- The application to amend the current Poisons Standard with respect to niclosamide (the Application)
- The 6 public submissions received in response to the pre-meeting public consultation (the Submissions)
- The advice received from the 38th meeting of the Advisory Committee on Chemicals Scheduling (the Committee)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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 SPF, and
- The Handbook.

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

Summary of Committee advice to the Delegate

The Committee recommended that the scheduling for niclosamide be amended as follows:[18]

Schedule 6 – New entry

NICLOSAMIDE **except** when included in Schedule 2 or 5.

Schedule 5 – New entry

NICLOSAMIDE in tablet or paste preparations for companion animals.

Schedule 2

NICLOSAMIDE for human therapeutic use.

Index – Amend entry

NICLOSAMIDE

Schedule 6
Schedule 5
Schedule 2

The Committee recommended an implementation date of **1 October 2024**, as there were no relevant marketed products and therefore no reason to delay the implementation of the decision.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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

Risks:

- Niclosamide has low toxicity in humans, cats and dogs with rare occurrence of adverse events.

Benefits:

- The potential benefits include use as a molluscicide in agriculture, subject to regulatory approval, and anthelmintic use in animals and humans.

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

- Niclosamide is a molluscicide for use in snail-infested rice bays.
- Niclosamide has limited anthelmintic use in veterinary and human medicine.

c) the toxicity of a substance

- Niclosamide has low acute toxicity, with potential for eye, and skin corrosion and respiratory exposure during mixing and spraying.
- Risk of toxic effects to humans can be minimised by use of appropriate personal protective equipment and adhering to correct measures during mixing and spraying.

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

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

- Niclosamide will be presented as an emulsifiable concentrate in plastic drums with tamper proof lids and will be diluted on site.
- As a veterinary therapeutic agent, niclosamide is presented in tablets and pastes.

e) the potential for abuse of a substance

- Nil.

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

- The potential for increased access in future for domestic use or novel therapeutic use may need to be considered in determining appropriate access.
- There is potential for environmental risk which is outside the purview of Poisons Standard and is addressed by the Australian Pesticides and Veterinary Medicines Authority (APVMA).

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

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

With regards to s 52E(1)(a) of the Act, Niclosamide is presently used in Australia as an anthelmintic medication to treat parasitic infections in animals and humans. Overseas, niclosamide is also used to control freshwater snails on crops. Although in Australia niclosamide has not been registered for use for snail control in agriculture, the Australian Pesticides and Veterinary Medicines Authority (APVMA) has recently received an application for a new molluscicide product that contains niclosamide as an active ingredient.

I have considered the 6 public submissions received during the pre-meeting consultation period, of which 5 supported the proposal and one opposed it. None of the respondents provided reasons for their support or opposition and as a result, the extent of my consideration is limited to noting that the submissions were generally in favour of the scheduling proposal.

Niclosamide is presently included in Schedule 2 for human therapeutic use, and unscheduled for all other uses. Regarding s 52E(1)(b), I note that the use of niclosamide in Australia is currently limited. There are 9 veterinary products containing niclosamide registered on the Australian Pesticides and Veterinary Medicines Authority's (APVMA) Public Chemical Registration Information System (PubCRIS) database. All these registered products containing niclosamide are co-formulated with either pyrantel or levamisole with the pyrantel products being unscheduled under the current Poisons Standard. I also note the Committee's advice that the use of niclosamide in a veterinary setting has largely been superseded by newer medicines such as praziquantel. However, I agree with the applicant that the potential hazards associated with the use of niclosamide warrant further examination, particularly considering the recent application for agricultural use.

I have reviewed the data received as part of the Application. Considering s 52E(1)(c) of the Act, I agree that the toxicity of niclosamide is consistent with the SPF factors for a Schedule 6 substance. While the substance has relatively mild acute toxicity by the oral and inhalational routes, niclosamide is potentially corrosive to the skin and eyes. The information that was presented as part of the application by the regulator (APVMA) of a prospective agricultural product, indicates that the risks to the user associated with the agricultural use of niclosamide could be adequately mitigated via the use of personal protective equipment and product labelling. I am of the view that appropriate safety directions, warning statements and first aid instructions would be developed by the regulator (APVMA) and together with the use of PPE, would mitigate the risk to users from possible exposure during handling, mixing and application of products containing niclosamide.

Further, in reference to s 52E(1)(d), I agree that niclosamide in tablets and pastes pose a lower risk as these formulations are less likely to come into contact with the skin and eyes of users of such veterinary preparations. I am of the view that a lower scheduling for such veterinary preparations is commensurate with the reduced risk, together with appropriate labelling by the regulator (APVMA). My decision is supported by the lack of adverse reaction reports associated with the currently registered niclosamide products for veterinary use, all of which are available as tablets or pastes. I therefore concur with the Applicant and the advice of the Committee that niclosamide in tablet and paste formulations for use in companion animals should be included in a new Schedule 5 entry in the Poisons Standard.

In relation to s 52E(1)(f), I note that niclosamide has been assessed as hazardous for aquatic wildlife. While information about environmental risk mitigation has been provided to the APVMA, environmental risks are outside the purview of the scheduling of substances under the Poisons Standard.

I also note that niclosamide is currently the subject of clinical investigations into the treatment of a range of conditions, including cancer and various infectious diseases in humans. The outcome of this research could lead to the development of new human therapeutic agents that may necessitate further consideration of the scheduling of niclosamide under the Poisons Standard.

I have decided that an extended implementation period is warranted, given that various registered niclosamide products will require labelling changes due to the amended scheduling.

Implementation date

1 June 2025

Interim decisions on proposed amendments referred to the Advisory Committees on Medicines and Chemicals Scheduling in joint session (ACMS-ACCS #36, March 2024)

Interim decision in relation to oxytetracycline

Proposal

The Delegate received an application to amend the Schedule 5 entry for oxytetracycline to include topical preparations for animals to treat superficial skin infections. These preparations are currently included in the Schedule 4 entry for the substance and are available by prescription only.

Interim decision

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

Materials considered

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

- The application to amend the current Poisons Standard with respect to oxytetracycline (the Application)
- The 23 public submissions received in response to the pre-meeting public consultation (the Submissions)
- The advice received from the 36th meeting of the Advisory Committee on Medicines and Chemicals Scheduling in joint session (the Committee)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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 MSD Veterinary Manual (the MSD Manual)
- The World Health Organisation's Critically Important Antimicrobials for Human Medicine 5th Revisions 2016
- The SPF, and
- The Handbook.

Summary of Committee advice to the Delegate

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

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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

Risks:

- The proposal may lead to increased antimicrobial resistance with an associated potential harm to human and animal health. Treatment needs to be limited to specific and susceptible bacterial infections.
- Oxytetracycline is an important first-line antimicrobial for many life-threatening infections across several species and there are implications for animal welfare if it is not used responsibly. There is also an increased risk of dosing errors.
- The proposal may lead to increased biosecurity and emergency animal disease risks when veterinary oversight is absent and an accurate diagnosis is not made, such as misdiagnosing Foot and Mouth Disease.
- The proposal presents the potential for increased inappropriate use of topical tetracycline instead of following best practice where treatment of a superficial wound infection should be first undertaken with an antiseptic.
- Risk of inappropriate and off label use.

Benefits:

- Oxytetracycline is a broad-spectrum antibiotic used to treat superficial infections and digital dermatitis in animals only. It is effective against a wide range of gram positive and negative bacteria and certain other micro-organisms like rickettsiae, mycoplasmas, and some protozoa.

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

- In Australia, oxytetracycline is not approved for human use but is used for a variety of infections in animals. Topically it may be used in the treatment of foot rot in sheep, digital dermatitis in cattle, and superficial skin infections caused by oxytetracycline sensitive organisms in pigs, sheep and cattle.
- Oxytetracycline is administered intravenously and intramuscularly for the management of a range of infections across a range of animal species.

c) the toxicity of a substance

- While oxytetracycline has negligible absorption through intact skin, there is evidence for some absorption through broken skin or if the area affected is highly vascular.
- Topical use of oxytetracycline is unlikely to cause allergic reactions as evidence for residues of antibiotics in foods causing allergic reactions is sparse. No information was provided regarding the risk of developing contact dermatitis.
- In humans, tetracyclines such as oxytetracycline in high doses have been associated with liver failure and are contraindicated in pregnant women (pregnancy Category D) and children under the age of 8. Veterinarians are advised not to apply near udders and teats to avoid human exposure through contaminated milk.

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

- There are many registered oxytetracycline products for animal use including injections and oral powders.
- There is currently one topical spray containing oxytetracycline registered for use in Australia for animal use, containing 33 mg/g oxytetracycline in an aerosol spray.

e) the potential for abuse of a substance

- Nil.

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

- In 2004 the Expert Advisory Group on Antimicrobial Resistance (EAGAR) supported the recommendation that the scheduling of the tetracycline group of antibiotics be retained as Schedule 4.
- It may be appropriate to review moderate to high risk tetracyclines under non-Schedule 5 environments.

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

I agree with the Committee's findings on the relevant provisions of section 52E of the Act. I have made an interim decision not to amend the Poisons Standard with regards to oxytetracycline. In making this decision I have balanced the potential benefits of increasing the access of topical preparations for animals to treat superficial skin infections in Australia against the potential risks, mainly those associated with misuse or overuse. I have decided veterinarian oversight remains essential to the appropriate use of this substance.

I have considered the 23 public submissions received during the pre-meeting consultation period of which 19 opposed the proposal and 4 supported it.

Interested parties were given the choice to indicate their support of opposition to the proposed amendments with or without providing a written component. Sixteen submissions with written responses opposed the proposal due to concerns in relation to misuse and subsequent antimicrobial resistance (AMR), biosecurity threats and animal welfare implications. The 4 submissions in favour of the proposal did not provide any reasons for support.

In relation to s 52E(b)(d) and (f) of the Act, oxytetracycline is a broad-spectrum bacteriostatic antibiotic commonly used for respiratory tract infections, urinary tract infections, and skin and soft tissue infections in animals. There are 2 dermatological products registered on the Australian Pesticides and Veterinary Medicines Authority's (APVMA) Public Chemical Registration Information System (PubCRIS). These products are applied topically to treat foot rot in sheep, dermatitis in cattle and superficial skin infections caused by oxytetracycline sensitive organisms in pigs, sheep and cattle. While there are no registered oxytetracycline products on the Australian Register of Therapeutic Goods (ARTG), other tetracyclines such as doxycycline and minocycline are used in humans in Australia. I note oxytetracycline is listed as a highly important antimicrobial by the World Health Organization as there is limited therapy for infections due to *Brucella* spp., *Chlamydia* spp. and *Rickettsia* spp..[19] Brucellosis is still found in the feral pig population in Queensland and northern New South Wales and can infect humans and dogs hunting and consuming feral pigs.[20]

Concerning s 52E(a) and (c) of the Act, I recognise oxytetracycline of itself poses some risks to human health and safety. Oxytetracycline is listed as a Category D medicine in the Therapeutic Goods

[19] Critically Important Antimicrobials for Human Medicine 5th Revisions 2016, World Health Organisation

[20] https://www.health.nsw.gov.au/Infectious/factsheets/Pages/brucellosis.aspx

Administration's (TGA) pregnancy database, for prescription medicines which have caused or are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage.[21] This is of particular concern when considering broadening access to topical oxytetracycline products for superficial skin infections in animals as there is a risk of milk contamination if applied topically on udders or teats and if it is not thoroughly washed off prior to milking or handling treated areas of the animal. While topical oxytetracycline preparations do not require special skills to apply, there are some eye and skin irritation risks to the user, especially when used in spray formulations, consistent with the notified classification of the European Chemicals Agency (ECHA). Allergic reactions due to residues of oxytetracycline in food are not expected to occur and there is no evidence of carcinogenic potential of oxytetracycline based on studies in rats and mice or during its extensive use in humans.

In relation to s 52E(a) of the Act, I have considered the risk of increased antimicrobial resistance to oxytetracycline from inappropriate use. Increased access to oxytetracycline as proposed in the Application via reduced scheduling, could lead to uses that are not approved indications or its use in other animal species. The risk of tetracycline resistance is well documented and poses broader risks to the efficacy of other tetracyclines used in humans.[22]

With this in mind, I find the use of oxytetracycline consistent with Schedule 4, Factor 7 of the SPF where the substance has contributed to, or is likely to contribute to, communal harm by developing resistant strains of microorganisms. Therefore, veterinarian involvement is critical for antimicrobial stewardship and the promotion of responsible use of oxytetracycline. I note when oxytetracycline was last considered for scheduling in 2004, the Expert Advisory Group on Antimicrobial Resistance (EAGAR) supported retaining the tetracycline group of antibiotics as Schedule 4 substances.

In addition to the risk of antimicrobial resistance, I am concerned that urgent and serious conditions could be misdiagnosed without veterinary involvement (s 52E(f) of the Act). I agree with the Australian Veterinary Association's (AVA) submission that Foot and Mouth Disease (FMD) is different from other dermatological diseases localised to the feet in cloven-hoofed animals and veterinary expertise is required to distinguish them[23]. FMD is highly contagious, potentially fatal and can have large scale effects on cloven hoofed animals if diagnosis is delayed. I am of the view increasing access to oxytetracycline as proposed, will pose a considerable risk for FMD to be mistaken for superficial skin infections and result in a delay in the proper diagnosis and treatment.

I have also considered the varying treatment protocols depending on the type or severity of footrot or other digital dermatoses in sheep and cattle. The MSD Manual and AVA submission highlighted first-line treatment for benign and virulent footrot in sheep is the use of an appropriate antiseptic footbath such as zinc sulfate. The MSD Manual states antibiotic sprays are not as effective as footbaths or soaking,[24] and I agree with the AVA submission that severe cases of virulent footrot may require parenterally administrated antibiotics. While I acknowledge in cattle topical oxytetracycline can be effective for treating digital dermatitis,[25] foot rot should be treated with systemic antimicrobials. I am of the view these ailments require veterinary intervention for accurate diagnosis before oxytetracycline is used which is consistent with Schedule 4, Factor 1 of the SPF.

Notwithstanding the concerns related to the ready access to veterinarians across Australia, I am of the view that veterinarian advice, and timely and appropriate use of antibiotics is critical in this situation to minimise the development of antimicrobial resistance within Australian livestock and the general human population as a whole. I understand once a veterinarian has established an initial relationship with the client and has sufficient knowledge of their flock or herd, they are permitted to supply Schedule 4 medications remotely such as via telemedicine. [26] There is also a comprehensive delivery

21 www.tga.gov.au/products/medicines/find-information-about-medicine/prescribing-medicines-pregnancy-database

22 https://pubmed.ncbi.nlm.nih.gov/8916553/

23 The Australian Veterinary Association's (AVA) prescribing guidelines

24 https://www.msdvetmanual.com/musculoskeletal-system/lameness-in-sheep/contagious-footrot-in-sheep

25 https://www.msdvetmanual.com/musculoskeletal-system/lameness-in-cattle/lameness-originating-in-the-hoof-in-cattle#Digital-Dermatitis_v80036287

26 https://www.ava.com.au/library-journals-and-resources/ava-other-resources/prescribing-guidelines/

network available in Australia.[27] With these factors in mind, I am reassured that a high level of animal welfare can be maintained.

For all these reasons, I find the potential risks to heavily outweigh the potential benefits if access to oxytetracycline was broadened as proposed for topical application to animal to treat superficial skin infections. Therefore, I have decided not to amend the Poisons Standard with regards to oxytetracycline.

Interim decision in relation to tranexamic acid

Proposal

The Delegate received an application proposing an exemption for topical cosmetic preparations containing up to 3% tranexamic acid from the Schedule 4 entry for the substance. At present, the scheduling exemption is limited to the derivative cetyl tranexamate.

Interim decision

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

Schedule 4 –Amend Entry

TRANEXAMIC ACID **except** in preparations containing 3% or less of ~~cetyl tranexamate hydrochloride~~ tranexamic acid for dermal cosmetic use.

Index – Amend entry

TRANEXAMIC ACID
~~cross reference: CETYL TRANEXAMATE~~

Schedule 4

Materials considered

- In making this interim decision, the Delegate considered the following material:
- The application to amend the current Poisons Standard with respect to tranexamic acid (the Application)
- The 9 public submissions, received in response to the pre-meeting public consultation (the Submissions)
- The advice received from the 36th meeting of the Advisory Committee on Medicines and Chemicals Scheduling in joint session (the Committee)
- Subsection 52E(1) of the Act, in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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 SPF, and
- The Handbook.

[27] https://auspost.com.au/content/dam/auspost_corp/media/documents/australia-post-in-regional-rural-and-remote-communities.pdf

Summary of Committee advice to the Delegate

The Committee recommended that the scheduling of tranexamic have its current Schedule 4 listing amended in the Poisons Standard as follows:[28]

Schedule 4 – Amend entry

TRANEXAMIC ACID except in preparations containing 3% or less of ~~cetyl tranexamate Hydrochloride~~ tranexamic acid for dermal cosmetic use.

Index – Amend entry

TRANEXAMIC ACID
~~cross reference: CETYL TRANEXAMATE~~

Schedule 4

The Committee recommended an implementation date of **1 October 2024** as exempting dermal cosmetic products containing 3% or less tranexamic acid is unlikely to disrupt existing supply or access to these products.

Members agreed that the relevant matters under subsection 52E(1) of the Act included: (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (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

Risks:

– The available evidence is that low concentrations of tranexamic acid for dermal cosmetic use are low risk. Exempting low concentrations for cosmetic use would be comparable to overseas exemptions.

Benefits:

– Tranexamic acid is used via oral and intravenous routes to prevent blood loss. The proposal relates to dermal cosmetic use where tranexamic acid is used to improve skin pigmentation.

– Cosmetic use of tranexamic acid to increase the uniformity of pigmentation, particularly on the face, could potentially improve the wellbeing of the user.

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

– Tranexamic acid is present in dermal cosmetic formulations.

– There appears to be widespread use of tranexamic acid use overseas (Europe, USA, Canada, NZ) and there is evidence that skin products containing tranexamic acid are already being sold in Australia, despite its current Schedule 4 status.

c) the toxicity of a substance

– Tranexamic acid at the proposed concentrations is not irritating to the eyes or skin and is not a skin sensitiser. It has low acute oral toxicity, is not likely to cause severe systemic effects, and is not genotoxic.

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

- Tranexamic acid is included in the TGA's Prescribing medicines in pregnancy database in category B1.

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

- The substance is proposed to be used in topical preparations, for example, serums, which usually have small volumes (50-100 mL) and low concentrations (up to 3%).

e) the potential for abuse of a substance

- Nil.

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

- Oral contraceptive users lack the capacity to self-diagnose melasma and are more likely to attribute symptoms to age-related skin darkening.
- Potential for inappropriate long-term use in dermal applications (use a skin lightening agent). The overlap for cosmetic preparations and emerging therapeutic applications could result in misdiagnosis of other skin pigmenting conditions.

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

I agree with the Committee's findings on the relevant provisions of section 52E of the Act. I have made the interim decision to amend the Poisons Standard with respect to tranexamic acid to exempt 3% tranexamic acid for dermal cosmetic use. The existing exemption for 3% cetyl tranexamate hydrochloride in dermal cosmetic preparations was introduced in 2013 in consideration of its lack of toxicity, systemic exposure and adverse effects. In making this decision I note that tranexamic acid similarly poses low risk of dermal toxicity, eye and skin irritation, and skin sensitisation at a 3% concentration.

I have considered the 9 public submissions received during the pre-meeting consultation period. Seven submissions supported the proposal and 2 opposed it.

Interested parties were given the choice to select from options to indicate their support or opposition to the proposed amendment without providing a written component. Two of the supportive submissions provided written responses and highlighted that tranexamic acid has low acute oral toxicity, does not cause skin or eye irritation or skin sensitisation, and poses negligible risk of abuse or misuse at the recommended dosage. They also noted that dermal cosmetic preparations of tranexamic acid are currently available internationally, including in New Zealand, US, Europe and Canada. The written submission in opposition to the proposal highlighted the lack of evidence of topical efficacy of tranexamic acid and noted that allowing non-efficacious substances in dermal cosmetic products will compromise the quality of the products.

In consideration of s 52E(1)(a) of the Act, dermal cosmetic preparation of tranexamic acid could provide benefits to consumer wellbeing through increasing the uniformity of skin pigmentation. I am in agreement with the Committee that low concentrations of tranexamic acid for dermal cosmetic use are low risk in nature and exempting low concentrations for cosmetic use would be align with international regulatory exemptions. Further, there is no evidence that cetyl tranexamte and tranexamic acid posed different risks in cosmetic preparations, and the scheduling approach should be consistent.

With regards to s 52E(1)(b) and (d) of the Act, in Australia tranexamic acid products are currently only registered and marketed for therapeutic uses. Tranexamic acid is used intravenously to prevent or treat excessive blood loss and orally in dental surgery to prevent excessive bleeding. The applicant proposed for tranexamic acid up to 3% concentration to be used in topical preparations, for example serums at 50-100 mL volumes. Exempting cosmetic preparation of tranexamic acid will not impact the

scheduling and availability of oral and intravenous preparations of tranexamic acid for therapeutic purposes.

In considering s 52E(1)(c) of the Act, I agree with the Committee and Applicant that tranexamic acid poses a low risk of eye and skin irritation and is not a skin sensitiser. Similarly, tranexamic acid poses a low risk of acute oral toxicity and does not pose a risk of genotoxicity and carcinogenicity. I also note that percutaneous absorption of tranexamic acid is low at the proposed recommended dosage and any resulting systemic exposure, even from regular use, is unlikely to cause adverse health effects. Finally, there are limited case reports of oral overdose of tranexamic acid. The risk of substance toxicity for tranexamic acid does not align with the SPF factors of any Schedule.

In considering other factors relevant to scheduling, s 52E(1)(f) of the Act, I have considered the Committee's concerns regarding the capacity for consumers to self-diagnose skin conditions such as melasma. I agree there is a risk of oral contraceptive users misdiagnosing melasma with age-related skin darkening. I also agree with the Committee that some cosmetic formulations, through suggestive product labelling and marketing, may make claims that are therapeutic in effect. The overlap for cosmetic preparations and emerging therapeutic applications could result in misdiagnosis of other skin pigmenting conditions. I also note the potential risks of inappropriate long-term use of dermal applications when used as a skin lightening agent. However, I remain of the opinion that at the recommended dosage the risks of substance misuse, dermal toxicity and skin sensitisation are low.

In summary, I am of the view that the risks posed by 3% or less dermal cosmetic preparations of tranexamic acid do not align with any of the Scheduling factors and support an exemption from scheduling.

Implementation date

1 October 2024

Therapeutic Goods Administration

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