Australian Government
Department of Health
Therapeutic Goods Administration

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

10 March 2022

TGA Health Safety Regulation

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

Contents

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

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

the interim decisions made by a delegate of the Secretary under regulation 42ZCZN in relation to proposed amendments to the current Poisons Standard which were referred to an expert advisory committee under subdivision 3D.2 of the Regulations in November 2021;

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 **11 April 2022.**

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.

2. Interim decisions on proposed amendments referred to the Advisory Committee on Medicines Scheduling (ACMS #36, November 2021)

2.1 Interim decision in relation to astodrimer sodium

Proposal

The applicant proposed amendments to the existing Appendix F and Appendix H entries for astodrimer to include new warning statements for preventative use, and to remove existing restrictions on advertising for preparations containing the substance (the **Proposal**).

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision not to amend the current Poisons Standard Appendix H entry in relation to astodrimer sodium. The Delegate has made an interim decision to amend the current Poisons Standard Appendix F, Part 3 as follows:

Appendix F, Part 3 – Amend Entry

POISON	WARNING STATEMENTS	SAFETY DIRECTION
ASTODRIMER SODIUM		
a) For the treatment and relief of bacterial vaginosis	63, 64, 69, 75, 109, 110	
b) For the prevention of recurrent bacterial vaginosis	63, 75, 109, 110	

The Delegate's interim decision differs from the applicant's proposal and the detailed reasons for the decision follow.

Materials considered

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

- The application to amend the current Poisons Standard with respect to astodrimer sodium (the **Application**);
- The 41 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations.
- The advice received from the 36th meeting of the Advisory Committee on Medicines Scheduling (the **Committee**);
- Subsection 52E(1) of *the Therapeutic Goods Act 1989* (Cth) (the **Act**), in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health;
- The Scheduling Policy Framework 2018 (the **SPF**), pursuant to paragraph 52E(2)(a) of the Act; and
- The Scheduling handbook: Guidance for amending the Poisons Standard.

Summary of Committee advice to the Delegate

The Committee recommended no change to the current Appendix H entry for astodrimer sodium.

The Committee recommended that the Appendix F entry for astodrimer sodium in the Poisons Standard be amended as follows:

Appendix F, Part 3 – Amend Entry

POISON	WARNING STATEMENTS	SAFETY DIRECTION
ASTODRIMER SODIUM		
a) For the treatment and relief of bacterial vaginosis	63, 64, 69, 75, 109, 110	
b) For the prevention of recurrent bacterial vaginosis	63, 75, 109, 110	

The Committee also recommended an implementation date of **1 June 2022**.

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

The reasons for the advice included:

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

- Astodrimer sodium is a low-risk substance which is well tolerated with proper use.
- Astodrimer sodium is the only non-prescription substance available for the treatment of bacterial vaginosis, and this application does not propose any change to its overall scheduling and availability.

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

- The proposed change to the Appendix F entry captures the broadening of the intended uses of the substance to include the prevention of recurrent bacterial vaginosis.

c) the toxicity of a substance;

- The formulated product has minimal systemic absorption following mucosal administration.

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

- As a Class IIa medical device the placement of new warnings on the labelling would not undergo pre-market review and could lead to confusion at the point-of-sale and point-of-use.
- The applicant's proposed new warning statements would be in conflict with current warning labels for treatment and relief of BV, leading to confusion as to proper use in the absence of clear directions and labelling, which will not be available for review prior to marketing of the product.
- The clinical rationale for the applicant's proposed warning statements regarding prolonged period of use in prevention of recurrent BV was not made clear in the application.

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

- There is likely to be advertising of products containing astodrimer sodium for the prevention of recurrent BV if the proposed change to the Appendix H entry is

accepted, leading to potential misuse in the general prevention of BV and prevention and/or other STIs.

- Advertising for uses unrelated to BV carries the potential for misuse or misdiagnosis of more serious conditions.
- Removal of restrictions to the Appendix H entry would permit advertising for unforeseen future indications.

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

Astodrimer sodium is a dendrimer with negligible systemic absorption following mucosal administration.[1] A vaginal gel containing astodrimer sodium 1% w/w appears on the Australian Register of Therapeutic Goods (ARTG) as a Class IIa medical device, with intended uses for the treatment of bacterial vaginosis (BV) and the prevention of recurrent BV. The applicant proposed multiple amendments to the Poisons Standard consistent with the indications and uses of this product, specifically the prevention of recurrent BV. I agree with the Committee's findings on the relevant provisions of section 52E of the Act and have made an interim decision to amend the Appendix F, Part 3 entry in relation to astodrimer sodium in the Poisons Standard but make no change to the current Appendix H entry. I have provided reasons for these decisions separately below.

In making this decision, I have also considered the three written public submissions received during the pre-meeting consultation period. One written response received was fully supportive of the Application, and two partially supportive. Interested parties were also given the choice to select from options to indicate their support or opposition to the Application without providing a written component. Thirty-eight (38) responses were received, with 16 supportive, five partially supportive and 17 opposed. These respondents did not provide reasons for their support or opposition and as a result, the extent of my consideration is limited to noting that the submissions were mixed, but generally in favour of the Application.

Proposed changes to Appendix F, Part 1

The applicant proposed two new Appendix F, Part 1 entries for inclusion in the Poisons Standard, which would then be used in an expanded Appendix F, Part 3 entry for astodrimer sodium. I agree with the Committee's finding that the proposed warning statements "Discuss longer periods of use (>2 weeks) with a healthcare provider" and "Do not use for more than 16 weeks unless a doctor has told you to" are contradictory, both with each other and when viewed in the context of the existing warning statements required for this substance. I have considered paragraphs 52E(1)(b), (d) and (f) of the Act, and the SPF guidance on Appendix F entries, and have formed the opinion that the benefits derived from these warning statements are not consistent with my view that prolonged treatment (16 weeks) with any Schedule 3 substance without medical review is against best practice. I also note that "healthcare provider" is not defined within the Poisons Standard, and I do not find it to be a useful addition to Appendix F, Part 1. For these reasons I do not consider these proposed warning statements appropriate for inclusion in the Poisons Standard.

Taking into consideration the factors consistent with paragraphs 52E(1)(a) and (f) and the SPF, I endorse the Committee's recommendation to include warning statement 75 ("Do not use for more than 7 days unless a doctor has told you to") in the new Appendix F, Part 3 entry regarding use of astodrimer sodium in prevention of recurrent BV.

[1] O'Loughlin, et al. 2010, Safety, Tolerability, and Pharmacokinetics of SPL7013 Gel (VivaGel®): A Dose Ranging, Phase I Study, *Sexually Transmitted Diseases*, February, Volume 37, Issue 2, pp 100-104

Proposed changes to Appendix F, Part 3

I have made an interim decision to include a new Appendix F, Part 3 entry for astodrimer sodium which reads "For the prevention of recurrent bacterial vaginosis". This entry will bring the Poisons Standard into alignment with the intended uses of products containing astodrimer sodium, consistent with paragraph 52E(1)(b) and(d) of the Act.

Proposed changes to Appendix H

I am of the opinion that expanding the Appendix H entry for astodrimer sodium to allow advertisement without restriction of specific indication carries with it an unacceptable risk to public health. Therefore, my interim decision is that the current Appendix H entry for astodrimer sodium remains appropriate.

I note that astodrimer sodium is the only non-antibiotic treatment for BV available without a prescription. Reducing the use of and reliance on antibiotics for the treatment of conditions such as BV aligns with the health priorities of the Australian Government.[2]

In making my interim decision, I have considered paragraphs 52E(1)(a), (b) and (f) of the Act. I am of the view that, while advertising may increase awareness of recurrent BV and a suitable treatment, such advertising is unlikely to be objective or unbiased. The advertising of astodrimer sodium for the long-term treatment of recurrent BV, and the consequent increase in use of this substance for this purpose, carries with it the potential to cause harm that outweighs the benefit of increased public awareness of the condition. BV is associated with serious complications such as pelvic inflammatory disease (PID) and an increase in the acquisition of sexually transmitted infections such as chlamydia, gonorrhoea, human immunodeficiency virus and herpes simplex type-2.[3] While I acknowledge that the warning statement "See your healthcare provider if you consider that you may be at risk of a Sexually Transmitted Infection (STI)" is currently required to appear on products containing astodrimer sodium, I must consider the possibility that some women using the substance for recurrent BV may not only be at an increased risk of serious sequelae, but they may be suffering from underdiagnosis or misdiagnosis of more serious conditions.

Further to this point, while reference to any serious disease or illness (termed 'restricted representations') in advertising regarding astodrimer sodium would not be permitted without TGA approval, products containing astodrimer sodium have been the subject of illegal advertising promoting its use in the treatment SARS-CoV-2[4]. Astodrimer sodium is also the subject of research for use in other conditions, most notably human immunodeficiency virus-1 and herpes simplex virus-2[5], and I note that the applicants of this scheduling proposal have conducted and published such research. Consistent with paragraphs 52E(1)(b) and (d) I note that a medicated male condom containing astodrimer sodium, indicated for the prevention of transmission of STIs, appears on the ARTG. I remain concerned that removing the current advertising restrictions from the Appendix H entry will remove an important control over a substance with a wide range of emerging uses.

I have considered the Pharmacy Guild of Australia's (the Guild) submission in support of the Application, stating that the proposed changes to the Appendix H entry are consistent with the product details for the astodrimer sodium vaginal gel. While I acknowledge this is correct, I

[2] 'Antimicrobial Resistance', 2021, Australian Government Department of Health; Australian Government Department of Agriculture, Water and the Environment, https://www.amr.gov.au/
[3] HealthDirect, *Bacterial vaginosis*, Australian Government Department of Health
[4] Therapeutic Goods Administration, Australian Government Department of Health https://www.tga.gov.au/media-release/starpharma-holdings-limited-fined-93240-alleged-unlawful-advertising-viraleze-relation-covid-19
[5] Paull J et al., 2021, Virucidal and antiviral activity of astodrimer sodium against SARS-CoV-2 in vitro, *Antiviral Research*, Volume 191

remain of the view that the benefits of increased advertising of the use of astodrimer in the prevention of recurrent BV are outweighed by the risk to broader public health from the underdiagnosis or misdiagnosis of this condition for the reasons outlined above. I note that the Pharmaceutical Society of Australia and the Australian Medical Association were both opposed to changes to the Appendix H entry.

In weighing the factors in paragraphs 52E(1)(a)(b) and (f) of the Act, the benefit of increased awareness for the prevention of BV, and the possible risks consistent with paragraphs 52E(1)(d) and (f) of the Act and the SPF guidance for Schedule 3 substances in relation to underdiagnosis or misdiagnosis of more serious conditions, I have formed the view that the current Appendix H entry remains appropriate.

Implementation date

1 June 2022

2.2 Interim decision in relation to flurbiprofen

Proposal

The applicant proposed that the Schedule 2 entry for flurbiprofen be amended to exempt preparations from scheduling when presented in containers of 15 mL or less, that contain 0.25% or 10 mg or less per dose of flurbiprofen and are labelled for the treatment of adults over 18 years (the **Proposal**).

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to amend Schedule 2 entry for flurbiprofen in the Poisons Standard as follows:

Schedule 2 – Amend Entry

FLURBIPROFEN in preparations for topical oral use when:

a) in divided preparations containing 10 mg or less of flurbiprofen per dosage unit **except** when:

   i) in a primary pack containing not more than 16 dosage units; and

   ii) labelled only for the treatment of adults and children over 12 years.

b) in undivided preparations containing 0.25 percent or less or 10 mg or less per dose of flurbiprofen **except** when:

   i) in a primary pack containing not more than 15 millilitres; and

   ii) labelled only for the treatment of adults over 18 years.

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FLURBIPROFEN

Schedule 4
Schedule 2

Materials considered

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

- The application to amend the current Poisons Standard with respect to flurbiprofen (the **Application**);
- The thirty-five (35) public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations;
- The advice received from the 36th meeting of the Advisory Committee on Medicines Scheduling (the **Committee**);
- Subsection 52E(1) of the *Therapeutic Goods Act 1989* (Cth) (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; and (f) any other matters that the Secretary considers necessary to protect public health;
- The Scheduling Policy Framework 2018 (the **SPF**), pursuant to paragraph 52E(2)(a) of the Act; and
- The Scheduling handbook: Guidance for amending the Poisons Standard.

Summary of Committee advice to the Delegate

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

Schedule 2 – Amend Entry

FLURBIPROFEN in preparations for topical oral use when:

a) in divided preparations containing 10 mg or less of flurbiprofen per dosage unit **except** when:

   i) in a primary pack containing not more than 16 dosage units; and

   ii) labelled only for the treatment of adults and children over 12 years.

b) in undivided preparations containing 0.25 percent or less or 10 mg or less per dose of flurbiprofen **except** when:

   i) in a primary pack containing not more than 15 millilitres; and

   ii) labelled only for the treatment of adults over 18 years.

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FLURBIPROFEN

Schedule 4
Schedule 2

The Committee also recommended an implementation date of **1 June 2022.**

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

The reasons for the advice included:

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

Benefits:

- Flurbiprofen demonstrates superiority over demulcent only lozenges (non-medicated) so a better option for self-medication of a sore throat
- Flurbiprofen provides pain relief via both anti-inflammatory and analgesic actions

Risks:

- Classified as a category C medication for pregnancy
- Hypersensitive reactions (may be fatal)
- Should not be used by children < 18 years

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

- For the relief of pain, swelling and inflammation associated with severe sore throats

c) the toxicity of a substance;

- The toxicity of flurbiprofen is considered very low: There is very low buccal systemic absorption and low bioavailability.

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

- Flurbiprofen 8.75mg/0.54mL solution pump actuated metered dose aerosol
- Maximum 5 sprays per day
- Proposal max 15mL as a Class IIb medical device, noting that the placement of new warnings on the labelling would not undergo pre-market review and could lead to confusion at the point-of-sale and point-of-use.

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

- Age restriction of 18 years and above, differs from the age restriction of 12 years for the flurbiprofen lozenge. The higher age limit is recommended as only adults (>18-years) participated in clinical trials.

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

I have made an interim decision to amend the Schedule 2 entry for flurbiprofen in the current Poisons Standard. This amendment would remove from Schedule 2 low-volume flurbiprofen throat sprays that are currently included in Schedule 2, permitting purchase of these products in general retail outlets if labelled for the treatment of adults. The detailed reasons for my decision follow.

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

In making my decision, I have taken into account all the public submissions received during the pre-meeting consultation period. I note the five written public submissions received during the pre-meeting consultation, including from the Australasian Medical Association, Pharmaceutical Society of Australia, Consumer Healthcare Products Australia, and the Pharmacy Guild of Australia. Interested parties were also given the choice to select from options to indicate their support or opposition to the Application without providing a written component. Thirty (30)

responses were received, with 17 supportive, four partially supportive and nine opposed. These respondents did not provide reasons for their support or opposition and as a result, the extent of my consideration is limited to noting that the submissions were mixed, but generally in favour of the Application.

In relation to paragraphs 52E(1)(a) of the Act, I consider that the benefits of low-volume throat sprays containing flurbiprofen outweigh the risks, given the data provided in the Application and the period of time such products have been available in as Pharmacy Medicines. A throat spray containing 8.75 mg/0.54 mL flurbiprofen was first listed on the ARTG in September 2015 and has been available in Australia as a Schedule 2 Pharmacy Medicine since 2016. Following the listing of this product, few adverse events have been reported, supporting my consideration that there is sufficient evidence to support the down-scheduling of flurbiprofen throat sprays and that throat spray preparations can be safely used by consumers without the need for healthcare professional input and oversight.

In further support of this decision, and in relation to paragraph 52E(1)(a) and (c) of the Act, I note that the low-dose flurbiprofen lozenge was found suitable for general sale (not scheduled) in Australia since 1 October 2020 (final decision ACMS #29, March 2020). I am satisfied that the evidence provided in the Application demonstrated comparable safety and toxicity of both the lozenge and the throat spray, whereby three sprays of the throat spray is bioequivalent to one lozenge and both dosage forms are well tolerated. In addition, the recommended maximum daily dose of 15 sprays, equivalent to 43.75 mg of flurbiprofen, is lower than the 70 mg of flurbiprofen or maximum 8 lozenges in a day, currently available for general sale. I am therefore of the view that low dose flurbiprofen throat sprays do not pose a significant risk of toxicity compared to the lozenge and would provide increased choice to consumers for relief of sore throat.

I note the issues raised by the Pharmacy Guild of Australia and Pharmaceutical Society of Australia in relation to paragraph 52E(1)(a), (c) and (d) of the Act, regarding limited benefit to public health and concerns of adverse reactions and toxicity, specifically in the context of differing dosage forms of the lozenge, throat spray and oral NSAIDs available for general sale. I have considered this risk and find that overdose by consuming the whole bottle (15 mL-~243 mg) would present with less toxicity than a prescribed oral dose of flurbiprofen (300 mg maximum). In addition, consuming a whole packet of flurbiprofen lozenges (140 mg) would also be less than the lowest oral form for prescribed flurbiprofen (150 mg). I consider that the risk of mistakenly taking multiple dose forms of flurbiprofen-containing products in combination with NSAIDs does not pose a significant risk of toxicity, due to the sufficient data indicating that flurbiprofen is locally acting with a low risk of systemic toxicity.

I note additional concerns arising from the public consultation in relation to paragraph 52E(1)(a), (c) and (d) of the Act, that flurbiprofen is listed as a Category C in pregnancy. Flurbiprofen is contraindicated in the third trimester of pregnancy due to the increased risk of premature closure of the foetal ductus arteriosus *in utero* and persistent pulmonary hypertension of the newborn infant.[6] In my view, appropriate and effective risk mitigation is already in place through other associated labelling requirements, such as the Required Advisory Statements for Medicine Labels (RASML) requirements for flurbiprofen (Schedule 1—Required Advisory Statements for Medicine Labels No. 6, 108) and Therapeutic Goods Order no. 92 (TGO92) (section 8(1)k(ii)). I am in agreement with the Application that flurbiprofen throat sprays carry the same warning statements as flurbiprofen lozenges and all topical and oral NSAIDs as required by the RASML regarding use in pregnancy, "Do not use at all during the last 3 months of pregnancy" and "Unless a doctor has told you to, do not use if you are trying to become pregnant or during the first 6 months of pregnancy". In addition, if use during pregnancy was to occur, the

[6] MIMSOnline, www.mimsonline.com.au/Search/AbbrPI.aspx?ModuleName=Product%20Info&searchKeyword=Flurbiprofen&PreviousPage=~/Search/QuickSearch.aspx&SearchType=&ID=56850004_2

risk associated with the use of flurbiprofen throat spray would be expected to be lower than with other unscheduled NSAIDs such as aspirin, as the flurbiprofen throat spray is a low-dose topical NSAID and systemic exposure is minimal due to relatively low absorption from the oral mucosa (10% of the equivalent dose of a flurbiprofen tablet).[7]

In consideration of paragraph 52E(1)(b) of the Act, I am of the view that that general sale of low volume flurbiprofen throat sprays will provide increased choice to consumers and meet a need not currently met by the flurbiprofen lozenge. Throat sprays tend to be used in situations where consumers are seeking rapid pain relief or to relieve more severe throat pain[8]. As severe sore throats commonly occur at night[9], a throat spray is likely to be the preferred dosage format as it allows rapid application and pain relief, without the need to stay awake while sucking on a lozenge. Hence, I am in view that there is a consumer need and benefit for increased access to this dosage form which is currently not satisfied by the unscheduled access to flurbiprofen lozenge. Moreover, the sales data demonstrates consumers' growing preference for purchasing medicated sore throat sprays in a grocery environment.[10,11]

In relation to paragraph 52E(1)(a) and (f) of the Act, I note the results of a randomised double-blind clinical trial[12] that showed clinical equivalence of the throat spray compared to the lozenge provided as part of the Application. As this data was obtained from patients over the age of 18 years, I agree that the higher age restriction for the throat spray is appropriate.

In considering the applicant's Proposal for the low-volume flurbiprofen throat sprays to be removed from Schedule 2 of the Poisons Standard, I have considered the 'reasonable safety' requirements set out in the Scheduling handbook. I consider that the low-volume flurbiprofen throat sprays meet the following criteria:

- The risks to health from the medicine are small and can be managed with packaging and labelling.
- Due to the low bioavailability the risk factors are low for incidence of adverse effects, interactions and contraindications.
- The risk of inappropriate use and misuse is negligible.
- There is little need to take any special precautions in handling.
- There is net public health benefit from wider availability for the consumer.

I note the concerns raised by the Pharmaceutical Society of Australia that the removal of flurbiprofen throat sprays from Schedule 2 does not align with the classification of flurbiprofen in other countries, whereby it is sold as a 'Prescription' or 'Pharmacy Medicine Only' in Ireland, USA, Canada, UK and New Zealand, and is not included in the WHO Model List of Essential Medicines 2019. However, in five countries including Australia, Denmark, and the Netherlands, the bioequivalent and therapeutically equivalent lozenges are available for general sale.

Upon careful consideration of the scheduling factors in paragraph 52E(1) of the Act, and the criteria for 'reasonable safety' set out in the scheduling handbook, I am satisfied that low-dose

[7] Gonzalez-Younes I, Wagner JG, Gaines DA, Ferry JJ, Hageman JM. *Absorption of flurbiprofen through human buccal mucosa*. J Pharm Sci. 1991; 80:820-823
[8] Incite. Global U&A sore throats, 2018.
[9] Winkle. Market research, Nurofen® dairy-based pain tracker. 2018
[10] Nielsen. Australian lozenge market, 2021.
[11] Nielsen. Australian sore throat spray market, 2021.
[12] Radkova E, Burova N, Bychkova V and DeVito R, *Efficacy of flurbiprofen 8.75 mg delivered as a spray or lozenge in patients with sore throat due to upper respiratory tract infection: a randomized, non-inferiority trial in the Russian Federation*, J Pain Res, 2017: 1591-1600

flurbiprofen throat sprays can be supplied at the general sales level with limited risk to public health and safety.

Implementation Date

1 June 2022

3. Interim decisions on proposed amendments referred to the Advisory Committee on Medicines and Chemicals Scheduling in joint session (Joint ACMS-ACCS #29, November 2021)

3.1 Interim decision in relation to cis-jasmone

Proposal

The applicant proposed the creation of new entries in Schedule 5 and Schedule 6 for cis-jasmone for agricultural use (The **Proposal**).

Interim Decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision create a new entry for cis-jasmone in Schedule 5 of the Poisons Standard as follows:

Schedule 5 – New Entry

> CIS-JASMONE when prepared and packaged as an agricultural chemical **except** when present as a fragrance.
>
> **Index – New Entry**
>
> **CIS-JASMONE**
> cross reference: (Z)-JASMONE
>
> Schedule 5

The Delegate's interim decision differs from the applicant's Proposal and the detailed reasons for the decision follow.

Materials considered

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

- The application to amend the current Poisons Standard with respect to cis-jasmone (the **Application**);
- The 23 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations.
- The advice received from the 29th meeting of the Advisory Committees on Medicines and Chemicals Scheduling in joint session (the **Committee**);

- Subsection 52E(1) of *the Therapeutic Goods Act 1989* (Cth) (the **Act**), in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters considered necessary to protect public health;
- The Scheduling Policy Framework 2018 (the **SPF**), pursuant to paragraph 52E(2)(a) of the Act; and
- The Scheduling handbook: Guidance for amending the Poisons Standard.

Summary of Committee advice to the Delegate

The Committee recommended that a Schedule 5 entry for cis-jasmone be created in the Poisons Standard as follows:

Schedule 5 – New Entry

> CIS-JASMONE when prepared and packaged as an agricultural chemical **except** when present as a fragrance.
>
> **Index – New Entry**
>
> **CIS-JASMONE**
> cross reference: (Z)-JASMONE
>
> Schedule 5

The Committee also recommended an implementation date of **1 June 2022**, given advice contained in the application that cis-jasmone is a new agricultural technical grade active constituent (TGAC) in Australia and scheduling is required to allow for approval and future registration of pesticide products.

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

The Committee's reasons for recommending the Schedule 5 entry were:

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

- The benefits include use of cis-jasmone as a pesticide for the purposes of this proposal.
- Cis-jasmone is also found naturally in a range of edible plants, with the highest concentration found in the jasmine plant. Other uses of cis-jasmone include food flavours, fragrances, cosmetics, cleaning products.
- Risks – low toxicological risks with some risk of eye and skin irritation. Low risk of misuse.

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

- Primary for pesticide use in agricultural activities, as per the purposes of this proposal.

- Cis–jasmone acts as a repellent to various insects; and may be a useful addition to pest management strategies to combat development of insect resistance from repeated use of synthetic chemical insecticides.
- There is potential for other uses (fragrance in agricultural products) and use outside of agricultural products, such as other fragrances, particularly at lower concentrations.
- Cis-jasmone may be used at lower concentrations as a fragrance in both agricultural and non-agricultural products. Other uses include food flavours, cosmetics, and cleaning products.

c) the toxicity of a substance

- Cis-jasmone fits the toxicity profile of a schedule 5 entry - low acute oral, dermal, and inhalational toxicity. Moderate eye irritant, slight skin irritant and not a skin sensitiser.
- No specific concentration cut-off was determined for the schedule 5 entry, to exempt the substance when used as a fragrance.

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

- APVMA label will address safety issues in relation to eye and skin exposure through PPE and safety instructions.
- Intended for commercial use as a seed treatment for protection against pathogenic nematodes in corn, cotton and soybeans. Product contains 9.2g/L cis-jasmone
- No packaging/labelling provided

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

- Inadvertent capture of unscheduled domestic pesticides when cis-jasmone is used as fragrance (rather than an active constituent).
- The term “plant protection production” is not a term the regulator (APVMA) uses for agricultural product registration. Use of this term may unintentionally capture other products.

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

I have made an interim decision to create a new entry for cis-jasmone in Schedule 5 of the Poisons Standard. This decision is made noting that the Application also proposed an additional Schedule 6 entry for the substance, but this was not supported for the reasons outlined below.

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

In making my decision, I have taken into account the public submissions received during the pre-meeting consultation period. I note the one written public submission received in opposition to the Application, which raised concerns about the inadvertent capture of products where cis-jasmone is included as a fragrance. In consideration of this issue and noting the substance’s toxicity profile, the interim decision proposes an amendment to the entry originally proposed by the applicant, to specifically exempt cis-jasmone when used as a fragrance. During the public submission period, interested parties were given the choice to select from options to indicate their support or opposition to the Application without providing a written component. Twenty-two (22) responses were received, with 17 supportive, two partially supportive and three opposed. These respondents did not provide reasons for their support or opposition and as a result, the extent of my consideration is limited to noting that the submissions were broadly supportive of the Application.

Cis-jasmone is an alicyclic ketone responsible for the characteristic smell of the jasmine plant *Jasminum polyanthum*. Furthermore, and relevant to my consideration under paragraph 52E(1)(a) of the Act, it is found naturally in a range of edible plants, including citrus, peppermint, raspberries, cinnamon and green tea. The substance is currently unscheduled with no limitations on its use or specific labelling requirements.

In relation to paragraph 52E(1)(c) of the Act and the SPF, I note that the toxicological profile of cis-jasmone provided in the application is consistent with a Schedule 5 classification, including:

- Acute oral toxicity LD_{50} between 1750 - 5000 mg/kg bw in rats,
- Acute dermal toxicity LD_{50} 5000 mg/kg bw in rats,
- Inhalational LC_{50} >2200 mg/m^3
- It is not a skin sensitiser, is a moderate eye irritant and a slight skin irritant. It does not appear to cause allergic skin reactions in animals or humans.
- Cis-jasmone is not considered to be mutagenic, carcinogenic or to have any genotoxic potential.

For the purposes of paragraphs 52E(1)(a), (b) and (e) of the Act, I agree with the Committee that occupational eye and skin exposure to cis-jasmone is reasonably foreseeable when in an agricultural chemical and harm to users can be reduced through the use of appropriate labelling consistent with a Schedule 5 but not a Schedule 6 poison.

I agree with the Committee's advice that, in relation to paragraph 52E(1)(f) of the Act, a Schedule 5 entry with no concentration exemption may inadvertently capture cis-jasmone when not present as an active ingredient, for example, when used as a fragrance in domestic pesticides and cleaning products. I agree with the Committee's recommendation to specifically exempt cis-jasmone when present as a fragrance from the Schedule 5 entry for this substance to be appropriate in view of the risks and the criteria outlined in the SPF (paragraphs 52E(1)(a) and 52E(2)(a) of the Act).

I note that the Joint FAO-WHO Expert Committee on Food Additives (JECFA) considers cis-jasmone to carry no safety concerns when used as a flavouring agent.[13] Moreover, jasmine as a natural extractive is currently categorised by the United States (US) Food and Drug Administration (FDA) as a "substance generally recognised as safe".[14]

I am of the view that the concentration of cis-jasmone when present in preparations as a fragrance is expected to be low. Therefore, a specific exemption for the substance when used as a fragrance in the Schedule 5 entry is appropriate at this time. The addition of the alternative nomenclature "Z-jasmone" to the index, will ensure the capture of new products as they are introduced to the market.

As this is a new active constituent proposed to be used in the agricultural sector, I propose an implementation date of 1 June 2022 to allow timely evaluation of potential products by the regulator.

Proposed implementation date

1 June 2022

[13] Joint FAO/WHO Expert Committee on Food Additives (JECFA) 2022, Food and Agriculture Organization of the United Nations (FAO) and World Health Organisation (WHO), https://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=2955

[14] United States (US) Food and Drug Administration (FDA), Code of Federal Regulations Title 21, https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=182.20

3.2 Interim decision in relation to cannabis and tetrahydrocannabinols

Proposal

The applicant proposed the amendment of the Schedule 8 entries for cannabis and tetrahydrocannabinols (THCs) to include therapeutic use on animals (except those bred for human consumption), along with a change to the Appendix D entry to prohibit possession of these substances other than in accordance with a legal prescription (the **Proposal**). Therapeutic use of cannabis and THCs is currently restricted to humans except for cannabidiol, which is available as a Schedule 4 (Prescription Only) medicine.

Interim Decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to not amend the current Poisons Standard in relation to cannabis and tetrahydrocannabinols. The detailed reasons for the decision follow.

Materials considered

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

- The application to amend the current Poisons Standard with respect to cannabis and THCs (the **Application**);
- The 116 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations;
- The advice received from the 29th Meeting of the Advisory Committees on Medicines and Chemicals Scheduling in joint session (the **Committee**);
- Subsection 52E(1) of *the Therapeutic Goods Act 1989* (Cth) (the **Act**), in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance;
- The Scheduling Policy Framework 2018 (the **SPF**), pursuant to paragraph 52E(2)(a) of the Act; and
- The Scheduling handbook: Guidance for amending the Poisons Standard.

Summary of Committee advice to the Delegate

The Committee recommended that no change be made to the current scheduling for cannabis and THCs.

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

The reasons for the advice included:

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

- The benefits associated with the use of cannabis and tetrahydrocannabinols in animals have not been adequately established and are likely outweighed by the risks presented by the toxic effects, as evidenced by veterinary presentations of pets inadvertently poisoned by cannabis.
- There is also the small but significant risk of inadvertent diversion to children if the product is in the form of an "edible treat".

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

- There is the potential use for animals in pain or for the management of epilepsy and anxiety disorders, however, the application failed to provide evidence of therapeutic value for cannabis or tetrahydrocannabinols in animals.

c) the toxicity of a substance:

- Although cannabis ingestion is rarely fatal to companion animals, it can cause significant morbidity.
- Significant reports of accidental ingestion of cannabis and cannabis-containing products by children, causing significant toxic effects.

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

- Appropriate therapeutic doses for these substances in animals have not been established.
- No specific products are registered for this purpose, although various formulations are possible, e.g. oils, gels, edibles.

e) the potential for abuse of a substance:

- The potential for abuse of products containing these substances has been established previously, as indicated by the existing entries in Schedules 8 and 9 of the Poisons Standard.
- The risk of misuse and diversion of animal medicines containing cannabis and tetrahydrocannabinols may be mitigated by the cost, addition of unpalatable flavourings, and the relatively small doses (particularly when intended for companion animals).

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

I have made an interim decision to not amend the current Poisons Standard in relation to cannabis and THCs. The basis of my decision is that the risks and toxicity of these substances outweigh the potential benefits, alongside a lack of demonstrated therapeutic evidence in animals, consistent with the SPF for Schedule 8 substances.

I agree with the Committee's findings on the relevant provisions of section 52E of the Act. However, I note that section 52AA of the Act provides that "the scheduling of substances allows restrictions to be placed on their supply to the public, in the interests of public health and safety. This is aimed at minimising the risks of poisoning from, and the misuse and abuse of, scheduled substances". Consequently, in my decision I have given weight predominately to the reasons related to the risk to public health and safety, rather than the purported benefits for animal treatment regimens.

In weighing up the benefits, and risks, including the toxicity and potential for misuse, I have taken into account the public submissions received during the pre-meeting consultation period. I note in particular the thirty-five (35) written submissions received in response to the pre-

meeting public notice. Of these written submissions, 30 submissions were in support of the Application, two partially supportive, and three opposed. Interested parties were also given the choice to select from options to indicate their support or opposition to the Application without providing a written component. Eighty-one (81) responses were received, with 59 supportive, 14 partially supportive and eight opposed. These respondents did not provide 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 Application.

In relation to paragraphs 52E(1)(a) and (b) of the Act, the Application relates to uses of the relevant substances for the treatment of a range of medical conditions in animals, including relief from chronic pain, treatment of anorexia, and the management of epilepsy and anxiety disorders. I note that reasons provided in support of the Application during the pre-meeting consultation referred to the potential for enhancing the health and wellbeing of veterinary patients, the expanding pool of research indicating the benefits of cannabis and THCs in the treatment of animals, and claims of the superior therapeutic outcomes associated with the therapeutic use of these substances compared to some existing treatments, e.g. opioids for the relief of chronic pain. I acknowledge the applicants' statement that veterinarians currently only have access to Schedule 4 preparations of cannabidiol, most often through compounded formulations, off-label use and products imported with permission from the Australian Pesticides and Veterinary Medicines Association (APVMA); and that increased access to Schedule 8 preparations of cannabis and THCs would enhance animal welfare by enabling access to veterinary products containing these substances that are of superior quality and safety than those presently available. I agree that the quality control of products containing Schedule 8 substances is well regulated and have no concerns that this would not also be true for veterinary preparations.

On balance with the Application and the consultations in support, I agree with the Committee's advice that the focus of considerations regarding this application should be whether cannabis and THCs have an established therapeutic value in treating animals, consistent with the SPF scheduling factors for Schedule 8 substances:

> *The substance has an established therapeutic value but its use, at established therapeutic dosage levels, is recognised to produce dependency and has a high propensity for misuse, abuse or illicit use.*

While the applicant provided a considerable volume of literature to support their Application, I note that the majority of these studies did not demonstrate established therapeutic value in animals. In addition, the majority of pharmacology and toxicity studies were not on cannabis and THCs but focused instead on cannabidiol, which is already available to veterinarians as a Schedule 4 medicine, and the analyses of the pharmacology and toxicity in many of these studies were extrapolated from studies in humans. I recognise the submission received from the Australian Veterinary Association (AVA), the primary representative body for veterinarians in Australia, in opposition to the Application. The AVA submission acknowledged increasing public interest in cannabis as a treatment option but noted that there is a lack of demonstrated clinical benefit or established protocols for administration of cannabis and THCs to animals, including uncertainty regarding appropriate dosages.

I have also considered the submission received from Racing Australia expressing concerns regarding the inconsistency between the Application and the prohibition of cannabis and THCs in equine racing. The submission indicated that: (i) approval of these substances for therapeutic use in horses would clash with the anti-doping laws instituted in the racing industry; and (ii) animal welfare would not be advantaged by the proposed scheduling changes due to the lack of evidence of efficacy for cannabis and THCs in a veterinary setting.

I have weighed the limited evidence of benefit of these substances against the risks in relation to paragraphs 52E(1)(a) and (c). In this regard, I am of the opinion that some of the risks are minimised by restricting the use of cannabis and THCs to animals not bred for human

consumption. I recognise that the lipophilicity of many cannabinoids, and the associated potential for bioaccumulation, may lead to introduction of these substances into human food supply chains if administered to animals bred for human consumption. I note that the exclusion of animals for human consumption is also likely to be necessary for compliance with Schedule 20 of the *Food Standards Code*, to ensure no chemical residues or contaminants associated with the therapeutic use of cannabis or THCs in animals are present in food. However, I also recognise the inconsistencies in the wording in the Application with respect to mechanisms used in other legislation, such as the *Agricultural and Veterinary Chemicals Code 1994*, which addresses "animals from food-producing species" rather than "animals bred for human consumption". This discrepancy may be problematic and would need to be addressed in the implementation if the proposed changes were adopted.

Of greater concern in relation to the risks of these substances, are reports of animals affected by cannabis-related toxication, through accidental exposure or misuse, presenting to veterinary hospitals.[15,16] I am concerned that the symptoms in such cases are reportedly unpleasant for the affected animal, and in rare cases death has occurred due to secondary complications. The AVA submission also commented on the typically non-lethal, but still significant, side-effects of cannabis use on animals, in particular the effects of THC. These concerns are compounded when considering paragraph 52(1)(d) of the Act, as I am of the view that the lack of established protocols or treatment regimens for the therapeutic use of cannabis and THCs in animals presents an unacceptable risk of increasing the incidence of these adverse reactions should these substances be made more readily available. Additionally, registered veterinary medicines are already available as treatment options for the indications included in the Application, and as yet, cannabis and THCs have not been shown to have additional efficacy or safety over these established medicines when used in animals.

In addition to adverse effects of cannabinoid toxicity in animals, I have considered the potential for accidental consumption of 'edibles' containing veterinary doses of cannabis and THCs by children, including research by Wylie et al[17] that shows that unintentional exposure of children to veterinary pharmaceuticals is common. Reports of such exposures show that the toxicity of THCs and cannabis can have severe adverse effects in children as they are unable to metabolise these substances as efficiently as adults.

Turning to paragraph 52E(1)(e) of the Act and addressing deliberate diversion and misuse, I agree with Committee's advice that these risks are likely to be mitigated through measures such as the inclusion of unpalatable flavouring agents in the formulations, cost, and the relatively small doses. These measures could address the risks of diversion once a potential veterinary product has been developed for regulatory approval.

I also agree with the Committee that the proposed changes to Appendix D for these substances are unnecessary, as access to products in Schedule 8 still requires a prescription by an appropriate medical practitioner, and therefore the exclusion of these substances from Appendix D goes against legislative requirements for Schedule 8 substances. I note that no other Schedule 8 substances are included in section 5 of Appendix D.

On balance, the limited demonstrated clinical benefit from the use of cannabis and THCs in animals is presently outweighed by the potential risks to animal industries, animals *per se* and young children. Therefore, I have decided to retain the current scheduling for these substances.

[15] *Vet and Human Toxicology*, 2004; *46*(1): 19-21.
[16] https://aspcapro.org/sites/default/files/z-toxbrief_0602.pdf
[17] *Clinical Toxicology,* 2019; 57:10, 855-866

3.3 Interim decision in relation to meloxicam

Proposal

The applicant proposed to create a new Schedule 6 entry for meloxicam that captures injectable preparations, at up to 2 per cent concentration, for the pre-surgical treatment of sheep undergoing husbandry procedures (the **Proposal**).

Interim decision

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

Materials considered

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

- The application to amend the current Poisons Standard with respect to meloxicam (the **Application**);
- The 333 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations;
- The advice received from the 29th Meeting of the Advisory Committees on Medicines and Chemicals Scheduling in joint session (the **Committee**);
- Subsection 52E(1) of *the Therapeutic Goods Act 1989* (Cth) (the **Act**), in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters considered necessary to protect public health;
- The Scheduling Policy Framework 2018 (the **SPF**), pursuant to paragraph 52E(2)(a) of the Act; and
- The Scheduling handbook: Guidance for amending the Poisons Standard.

Summary of Committee advice to the Delegate

The Committee recommended that no change be made to the current scheduling for meloxicam.

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

The reasons for the advice included:

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

Risks:

– The risks associated with the proposal include inadvertent or intentional self-administration, topical effects including hypersensitivity due to exposure upon administration, and exposure to meloxicam via the food chains in the event of failure in food controls.

- Some occupational exposures for topical consideration.

Benefits:

- Relief of pain, inflammation and discomfort for sheep associated with animal husbandry procedures such as castration, tail docking and mulesing.

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

- Meloxicam in this instance is used in routine husbandry procedures, given as a single subcutaneous injection to sheep. However, injectable meloxicam is also used in several other species including those bred for human consumption.

c) the toxicity of a substance:

- Meloxicam generally has a good safety profile. Topical use of meloxicam in humans is associated with dermal effects such as irritation, erythema, itching and rash, and rarely dyspnoea, nausea, dyspepsia, abdominal pain, gastritis, contact dermatitis and peripheral oedema.

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

- The product related to the application is a 20 mg/mL meloxicam injection in a 250mL multi-dose glass vial. Several other pack sizes are available for the current prescription-only product.

e) the potential for abuse of a substance:

- Use of the product to treat species other than sheep without veterinary oversight is possible under the proposed amended scheduling.
- The potential of the increased availability of meloxicam to impact the integrity of the thoroughbred racing industry. Horses may be given meloxicam to mask pain so that they can race despite injury. In addition, human mental health may also be affected through financial losses resulting from betting on unfit horses included in the field.
- Potential for diversion is low.

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

- The likelihood of regulatory failure given the lack of enforceable jurisdictional controls on who may be supplied a Schedule 6 product.
- The lack of consistency in increasing the availability of injectable meloxicam as a Schedule 6 poison, while the lower risk buccal preparation still requires a prescription.

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

I have made an interim decision to not amend the current Poisons Standard in relation to meloxicam. 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 taken into account section 52E(1)(b) of the Act and note that meloxicam is a non-steroidal anti-inflammatory with applications for both humans and animals, and all uses of the substance are currently captured under the Schedule 4 (Prescription Only) entry in the Poisons Standard. The Proposal seeks to create a new Schedule 6 entry for injectable preparations containing not more than 2 per cent of meloxicam, for the pre-surgical treatment of sheep for particular

husbandry procedures. Such a proposal would enable farmers access to meloxicam without a prescription for use in routine animal husbandry procedures, provided the medicine is supplied by a licenced wholesale provider.

In consideration of section 52E(1)(c) of the Act, the Application states that meloxicam has a moderate toxicity based on acute oral, intravenous and intraperitoneal studies. Since 2012, the Database of Adverse Event Notifications (DAEN) has recorded 137 reports of reactions that may have been associated with the use of meloxicam. Most of these reactions were gastrointestinal or dermatological in nature. I note with interest that between 2015-2020, there were 74 reports of serious incidents related to animal health associated with the use of meloxicam recorded in the Australian Pesticides and Veterinary Medicines Authority's Adverse Experience Reporting Program (AERP) database. In consideration of section 52E(1)(a) and (c) of the Act, I am of the view that these reports are a significant indicator of the risks associated with the use of this substance in a veterinary setting, especially as the administration of the drug is currently permitted only with the oversight of a veterinarian. Removal of this oversight via a Schedule 6 classification for meloxicam has the potential to increase the number of adverse events associated with this substance.

I agree with the Committee that there are no significant barriers to the access of meloxicam for veterinary use that would be addressed by creation of a new Schedule 6 entry, as preparations of meloxicam are presently available at low cost with a valid prescription. I also note that meloxicam continues to be regulated as a prescription-only medicine in all major international markets, including the USA[18], UK[19], Ireland[20], Canada[21] and New Zealand[22]. The rescheduling of meloxicam in any form would therefore be out of alignment with regulatory controls that are in place in these countries.

In relation to section 52E(1)(f) of the Act, I observe that under the Proposal, other preparations of meloxicam such as those for buccal administration would continue to be available only with a valid prescription. This would be inconsistent with the risks associated with each formulation type, as injectable formulations potentially have a higher risk profile due to the inherent health risks such as the potential for needlestick injuries. I agree with the Committee that the rescheduling of injectable meloxicam should also include preparations presenting lower risk, or else the scheduling remaining unchanged.

With regards to section 52E(1)(e) of the Act, I have doubts regarding the implementation of the proposed changes, in particular the potential for diversion to animals other than sheep for purposes other than those specified in the Application. The potential for intentional or inadvertent misuse of meloxicam under a Schedule 6 classification is significant, and given the toxicity profile of the substance, poses an unacceptable risk to animal welfare. I have also considered the potential for diversion of veterinary preparations of meloxicam to humans, however deem this to be less likely as preparations for human use are readily available.

I have considered the 232 written submissions received in response to the pre-meeting public notice, the majority of which were opposed to the Application (229 out of 232). Many of these submissions expressed similar concerns, including:

[18] United States (US) Food and Drug Administration (FDA), Drugs@FDA, https://www.accessdata.fda.gov/scripts/cder/daf/
[19] UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicines Agency (EMA), electronic medicines compendium (emc), https://www.medicines.org.uk/emc/
[20] Irish Medicines Board, Heath Products Regulatory Authority (HPRA) https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/
[21] Health Canada, Government of Canada, https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[22] MEDSAFE, New Zealand Ministry of Health, https://www.medsafe.govt.nz/profs/class/classintro.asp

- the lack of evidence that the current scheduling imposes barriers to the access of meloxicam or adversely impacts animal welfare,
- the lack of clarity regarding how the use of meloxicam will be restricted to sheep under the proposed Schedule 6 classification, and the hazards associated with misuse or diversion under the proposed rescheduling, and
- the lack of controls on advertising of Schedule 6 substances, which would create a conflict with the controls applied to advertising of Schedule 4 preparations of meloxicam.

I have noted in particular submissions received from the Australian Veterinary Association (AVA) and a number of special interest groups affiliated with the AVA, as well as the submission from Racing Australia, all of which opposed the Application. These bodies argued that the current scheduling of meloxicam did not unduly restrict access, and that reducing veterinary oversight carried the potential for diversion and misuse, both accidental and deliberate.

Interested parties were also given the choice to select from options to indicate their support or opposition to the Application without providing a written component. One-hundred-and-one (101) responses were received, with 19 supportive, two partially supportive, and 80 opposed. These respondents did not provide reasons for their support or opposition and as a result, the extent of my consideration is limited to noting that the submissions were mixed, but generally opposed to the Application.

I conclude that any benefits to increasing the availability of injectable meloxicam through a new Schedule 6 entry are outweighed by the risks associated with rescheduling, and therefore have decided to not amend the Poisons Standard with respect to meloxicam.

3.4 Interim decision in relation to choline salicylate

Proposal

The applicant proposed the creation of a new Schedule 3 entry for choline salicylate for human therapeutic or cosmetic use (the **Proposal**). Choline salicylate is currently captured in the Poisons Standard as a derivative of salicylic acid, of which dermal preparations containing greater than 40 per cent of the substance are captured in Schedule 3. Other dosage forms and lower concentration dermal preparations are not currently scheduled.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to create a new entry for choline salicylate in Schedule 2 of the Poisons Standard as follows:

Schedule 2 – New Entry

CHOLINE SALICYLATE for oromucosal preparations.

Index – New Entry

CHOLINE SALICYLATE

Schedule 2

The Delegate's interim decision differs from the applicant's Proposal and the detailed reasons for the decision follow.

Materials considered

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

- The application to amend the current Poisons Standard with respect to choline salicylate (the **Application**);
- The 28 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations;
- The advice received from the 29th meeting of the Advisory Committee on Medicines and Chemicals Scheduling in joint session (the **Committee**);
- Subsection 52E(1) of the *Therapeutic Goods Act 1989* (Cth) (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 Scheduling Policy Framework 2018 (the **SPF**), pursuant to paragraph 52E(2)(a) of the Act; and
- The Scheduling handbook: Guidance for amending the Poisons Standard.

Summary of Committee advice to the Delegate

The Committee advised that a new Schedule 2 entry for choline salicylate be created in the Poisons Standard as follows:

Schedule 2 – New Entry

CHOLINE SALICYLATE for oromucosal preparations.

Index – New Entry

CHOLINE SALICYLATE

Schedule 2

The Committee also recommended an implementation date of **1 February 2023**, due to consultation and review of products by 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:

- The risks associated with prolonged use and overuse of teething gels containing choline salicylate include salicylate toxicity and Reye's syndrome in young children.

Benefits:

- Relief of pain, inflammation and discomfort associated with teething, mouth ulcers/sores and new dentures or braces.

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

- There are currently eight registered therapeutic goods in the ARTG for relief of pain, inflammation and discomfort associated with teething, mouth ulcers/sores and new dentures or braces. However, the *Therapeutic Guidelines* do not recommend use of the substance for teething.
- Instructions for use vary, directing consumers to use from between three-hourly without any restrictions in the number of doses in a 24 hour period, to a maximum of six doses in 24 hours.

c) the toxicity of a substance

- Salicylic toxicity is expected with acute exposures to greater than 150 mg/kg or chronic exposures of greater than 100 mg/kg/day aspirin equivalents of salicylate.

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

- Seven of the eight medicines in the ARTG contain 87 mg/g choline salicylate and are available in pack sizes of 15 g, 20 g or 30 g. One medicine contains 90 mg/g choline salicylate and is available in 10 g pack size.
- Labelling is regulated by the TGA and includes appropriate dose rates and warnings e.g. two RASML statements. Stronger warning may be required.

e) the potential for abuse of a substance

- Low potential for abuse.

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

- Low likelihood but moderate to high consequences from misuse.
- Overuse and inappropriate use to be noted, but little evidence to support serious adverse events.

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 considered the eight written public submissions received during the pre-meeting consultation period. Two written responses received were fully supportive of the Application, two partially supportive and four opposed. Interested parties were also given the choice to select from options to indicate their support or opposition to the Application without providing a written component. Twenty (20) responses were received, with 13 supportive, three partially supportive and four opposed. These respondents did not provide 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 Application

In relation to paragraphs 52E(1)(a) and (c) of the Act, I concur with the concern raised by the applicant relating to overuse of products containing choline salicylate, leading to toxicity. I note that the Pharmaceutical Society of Australia (PSA), supporting the Application, stated in their submission that toxicity concerns regarding choline salicylate are not new and that the substance has continued to be available without restriction at significant concentrations. The PSA submission also identified that a low level of exposure to this substance can cause adverse events, and therefore having a pharmacist involved in the supply of choline salicylate would improve patient safety.

I note that the Pharmacy Guild of Australia also supported the Application, stating that the risks associated with choline salicylate use, especially in children, outweigh the benefits of use and current availability of the substance. In considering paragraph 52E(1)(b) of the Act, I note that choline salicylate is present in several teething products, contrary to the *Therapeutic Guidelines - Guidance for medical practitioners managing oral and dental issues* which recommends that teething gels (irrespective of choline salicylate content) should not be used in infants due to the lack of evidence of efficacy and the potential for harm.[23]

Based on these concerns, I have decided that choline salicylate should be included in a schedule of the Poisons Standard. I have therefore considered the SPF criteria to determine the relevant schedule for this substance. I am of the view that choline salicylate best fits the scheduling factors for Schedule 2 as set out in the SPF:

- The quality use of the medicine can be achieved by labelling, packaging, and/or provision of other information; however, access to advice from a pharmacist should be available to maximise the safe use of the medicine.
- The risk profile of the medicine is well-defined, and the risks can be identified and managed by a consumer through appropriate packaging and labelling, including consultation with a health professional if directed by labelling.

In support of placement within Schedule 2, and consistent with paragraph 52E(1)(e) of the Act, Reckitt Benckiser (Australia) Pty Limited noted in their submission that the New Zealand medicine regulator (MedSafe) has instituted restrictions on the sale of choline salicylate products (containing 10 per cent or less and in pack sizes of 15 grams or less). [24] I note that these controls are broadly equivalent to the Schedule 2 entry in the Poisons Standard. I also acknowledge the submissions from Accord Australasia and Consumer Healthcare Products Australia who opposed the Application on the basis that the scheduling should align with New Zealand.

I acknowledge the submissions opposing the Application, stating that the safety issues associated with oromucosal use of choline salicylate are rare and typically limited to use in children under the age of 18 months. The submissions also expressed concern that a scheduling change would capture choline salicylate products used for the relief from pain of mouth ulcers or dentures in adults and older children, and any schedule change should relate to teething products only. While taking these concerns into account, I consider that access to these products will not be unduly restricted through inclusion in Schedule 2. I am also of the opinion that scheduling controls structured around indications, such as allowing products for mouth ulcers or dentures to remain unscheduled, would lead to consumer confusion. A product marketed for mouth ulcers would have a greater accessibility to one indicated for teething pain, with different labelling instructions despite having a similar formulation and no instructions for use in teething, despite it possibly being used for this purpose. In my view, this situation would make the use of this substance more unsafe and as a result, I have chosen not to include a specification for use, or an age restriction in the Schedule 2 entry.

In relation to paragraphs 52E(1)(e) and (f) of the Act, I have determined that although there is low potential for abuse of choline salicylate, there is evidence of inappropriate use and misuse through overuse. I note that inclusion in Schedule 2 does not ameliorate accidental exposure and overdose rates. Similarly, in their submission the Australian Medical Association (AMA) were of the view that a change to the scheduling of this substance may not provide sufficient protection from adverse events. However, I consider the scheduling factors for Schedule 2

[23] Therapeutic Guidelines (eTG Complete) https://tgldcdp.tg.org.au/viewTopic?topicfile=management-of-dental-problems-for-medical-practitioners&guidelineName=Oral%20and%20Dental&topicNavigation=navigateTopic#toc_d1e682

[24] 'Minutes of the 66th meeting of the Medicines Classification Committee', MEDSAFE, New Zealand Ministry of Health, https://medsafe.govt.nz/profs/class/Minutes/2021-2025/mccMin11May2021.htm

should remedy these issues by ensuring that consumers can seek consultation with a pharmacist if concerned about the appropriate usage of the product.

In making this interim decision to schedule choline salicylate in Schedule 2 (Pharmacy Medicine) rather than Schedule 3 (Pharmacy Only Medicine), as proposed by the applicant, I am of the opinion that the Proposal would unduly restrict access for rural and remote communities, as licenced stores can stock Schedule 2 medicines, but not Schedule 3. In considering paragraphs 52E(1)(a) and (f) of the Act, the benefit of products containing this substance for relief of pain, inflammation and discomfort associated with mouth ulcers/sores and new dentures or braces, outweigh the risks of inappropriate use and misuse in the context of rural and remote community access, and should still be made accessible in these areas.

Balancing section 52E of the Act and the SPF, I concur with the concerns raised by the applicant relating to overuse of products containing choline salicylate, leading to toxicity; however, I am also of the view that a Schedule 3 entry would unduly restrict choline salicylate when used for other indications and in rural and remote communities. In consideration of the public submissions received in response to the pre-meeting public consultation, and advice from the Committee, I find that the risk of inappropriate use and misuse from overuse warrants a Schedule 2 entry in the Poisons Standard. I am of the opinion that advice from a pharmacist through placing choline salicylate in Schedule 2 is sufficient to maximise safe use.

Due to these changes impacting currently marketed consumer products, and to allow an appropriate transition period for compliance of industry, I have decided on an implementation date of 1 February 2023.

Implementation date

1 February 2023

4. Interim decisions on proposed amendments referred to the Advisory Committee on Chemicals Scheduling (ACCS #32, November 2021)

4.1 Interim decision in relation to chromates and chromium trioxide

Proposal

The applicant proposed that the Schedule 6 entries for chromates and chromium trioxide be amended to exempt articles where the proportion of chromates (or chromium) does not exceed 0.1% w/w of the article (the **Proposal**). In this application 'chromates' refers to three hexavalent chromium-containing compounds: dichromium tris (chromate), strontium chromate and chromic acid.

Interim Decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to not amend the Schedule 6 entry in the current Poisons Standard in relation to chromates and chromium trioxide. A new entry will be created in Appendix A of the Poisons Standard as follows:

Appendix A – New Entry

TREATMENT LAYERS OF COATED METAL ARTICLES for the collection of drinking water when compliant with the requirements of the Australian Standard AS 4020:2018 *Testing of products for use in contact with drinking water*.

Materials considered

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

- The application to amend the current Poisons Standard with respect to chromates and chromium trioxide (the **Application**);
- The 21 public submissions received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations;
- The advice received from the 32nd Meeting of the Advisory Committee on Chemicals Scheduling (the **Committee**);
- Subsection 52E(1) of the *Therapeutic Goods Act 1989* (Cth) (the **Act**), in particular (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health;
- The Scheduling Policy Framework 2018 (the **SPF**), pursuant to paragraph 52E(2)(a) of the Act; and
- The Scheduling handbook: Guidance for amending the Poisons Standard.

Summary of Committee advice to the Delegate

The Committee recommended that no change be made to the current scheduling for chromates and chromium trioxide.

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

The reasons for the advice included:

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

- The substances have several properties which are of concern: carcinogenicity, skin sensitising, mutagenicity, respiratory sensitising and suspected reproductive toxicity. The substances are currently listed in Schedule 6 of the Poisons Standard and thus present a serious risk which has already been noted by the TGA and other regulators.
- Benefits relate to reduced labour for maintenance of structures. This could mean lower exposure to the substances through maintenance activities. Limited evidence was provided by the applicant to substantiate this benefit.

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

- Chromates are included in pre-treatment and primer layers of painted metal articles to prevent corrosion and improve durability of the products. These are used in roofing, walling, and guttering which may be plumbed into rainwater

tanks for drinking water collection. Other applications include façade panels, air conditioner panels, cool room panels, fences, garage doors, garden sheds.

- Chromates are included in a passivation layer on the outer surface of galvanised metal articles. The galvanised metal products are used in roofing, walling, guttering which may also be plumbed into rainwater tanks for drinking water collection. Other applications for these galvanised articles include structural applications, purlins, structural decking, house framing, fence posts/rails, air conditioning panels.

c) the toxicity of a substance:

- The toxicity of chromates and dichromates as water soluble toxins via multiple routes of administration is well characterised. This application does not seek the rescheduling of chromates as a group and rather seeks to make chromates not scheduled when a component of treatment layers on coated metal articles.
- Chromium (IV) compounds are classified for Carcinogenicity (cat 1B) and Skin sensitisation (cat 1) (HCIS 2021). This is consistent with the criteria outlined in SPF Chapter 3 for schedule 6.
- Chromium trioxide is classified Acute toxicity (cat 1), Skin corrosion (cat 1), STOT (repeat cat 1), Respiratory sensitisation (cat 1), Skin sensitisation (cat 1), Carcinogenicity (cat 1A) and Reproductive toxicity (cat 1B) (HCIS 2021).

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

- The substances will be applied by the manufacturer to metal articles. Information on the hazardous nature of the substances will be provided through the product safety data sheet which states: "*Pre-painted steel should not be sanded, ground or otherwise abraded, in any operation that will penetrate the surface coating and create airborne dust. Penetrating or removing the primer layer by sanding or grinding may release dust particles containing strontium chromate. Strontium chromate is classified as a carcinogen category 1 (Known or presumed human carcinogens) according to SafeWork Australia. For processing operations that generate dust or fumes, the use of engineering controls may be necessary to maintain air concentrations below the relevant National Exposure Standards*."
- This information will not be made available at the retail level as the applicant suggests that the general public will not be heavy users of the materials.
- The propensity of the general public to use these materials through DIY activities may be underestimated by the applicant.

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

- Coated metal articles such as those included in the application are not appropriately addressed through the Poisons Standard.
- There is a reasonable potential for abuse of the substance through sanding and grinding of the metal articles by the general public who have not been provided with the safety information.

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

I have made an interim decision to not amend the current Poisons Standard in relation to chromates and chromium trioxide as proposed by the applicant, and instead create a new entry in Appendix A to exempt the specified articles from scheduling based on my assessment of the associated risks to public health. The detailed reasons for my decision follow.

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

In making my decision, I have taken into account all the public submissions received during the pre-meeting consultation period. I note that no written submissions were received during the public consultation period for the Application. Interested parties were given the choice to select from options to indicate their support or opposition to the Application without providing a written component. Twenty-one (21) responses were received, with 13 supportive, two partially supportive and six opposed. These respondents did not provide 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 Application.

I note that the Proposal is to amend the Schedule 6 entries for chromates and chromium trioxide to exempt small amounts of chromium compounds (less than 0.1% w/w) when present in the treatment layers of coated metal.

With regards to Section 52E(1)(c) of the Act, I note that the pre-treatment layer identified in the Application can contain up to 20% hexavalent chromium. The Application acknowledges that the toxicological profile of hexavalent chromates aligns with the Schedule 6 factors as outlined in the SPF. This profile is of particular concern with regards to Section 52E(1)(b) of the Act, as the finished materials containing these substances in coatings are used in a wide variety of industrial settings, including those exposed to rainwater, such as roofing, walling and guttering. However, I have noted the application's key statement that there is an inherent reduction of risk of exposure to chromates and chromium trioxide when presented as coatings, as the chemical bonding involved in the coating process is distinct from other coatings such as paints. The potential risk of toxicity to humans consistent with a Schedule 6 entry is not anticipated to arise if these articles are manufactured to an appropriate quality, that is, the integrity of the article and its coating are maintained.

In this light, I agree with the Committee's concerns regarding whether coated metal articles such as those that are the subject of the Proposal are within the scope of scheduling, and consider that the risk of chromates in these articles is not appropriately addressed through amendment of the Schedule 6 entry. Rather, articles of this type that are manufactured to acceptable quality and standards to prevent leaching of the chromates are more appropriately exempted from scheduling.

In this context, and taking into account that the primary public health risk associated with these articles is consumption of drinking water after it has been in contact with the surface, I note the reference to chromium in Australian Standard AS 4020:2018 *Testing of products for use in contact with drinking water*. This standard includes reference to the Australian Drinking Water Guidelines' maximum allowable concentration of 0.05 mg/L of chromium.

Therefore, the primary health risk associated with the use of chromates in these articles can be mitigated by compliance with this Australian Standard, and articles compliant with this standard are, in my view, appropriately exempt from scheduling.

I note the Committee's advice regarding references supplied by the applicant that purport to show that the risk of leaching of chromates from pre-treatment layers is low, consistent with not being entered in Schedule 6. While the overall findings of these studies were varied, I agree with the Committee that there are several shortcomings when attempting to relate them to the Proposal. Most importantly, there was a lack of speciated data regarding hexavalent chromium, the primary analyte of concern related to the Proposal. The lack of sufficient time frames between measurements made in some of the studies, in order to assess possible degradation of the surface layers, was also of concern. Nevertheless, I am satisfied that the risk to human health of exposure to chromates from relevant articles that comply with AS 4020:2018 does not require control through scheduling and therefore they should be exempted.

In summary, I am of the view that the proposed amendment to the Schedule 6 entry for chromates may not be the appropriate mechanism in this matter, as the public health risk associated with the use of chromates in these materials is already adequately addressed by the manufacturing standards. I agree with the comparison made by the Committee to the entry for glazed pottery in Appendix A, which contains items deemed to be unsuitable for control by scheduling. With this in mind, I have decided to create a similar entry in Appendix A for treatment layers of coated metal articles when complying with the requirements of the Australian Standard 4020:2018 *Testing of products for use in contact with drinking water*.

I have decided on a delayed implementation date for this amendment to allow industry time to make any necessary adjustments.

Proposed implementation date

1 October 2023