Australian Government
Department of Health
Therapeutic Goods Administration

Consultation: Proposed amendments to the Poisons Standard – ACCS, ACMS and joint ACCS/ACMS meetings, November 2021

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

We have changed the way to make submissions.

Submissions now should be provided through our consultation hub. Any submission about any of the proposals to amend the Poisons Standard will be considered at the next meeting of the Advisory Committee on Medicines Scheduling (ACMS), meeting of the Advisory Committee on Chemicals Scheduling (ACCS), or a joint meeting of these two committees.

This consultation closes on 7 October 2021.

Scheduling amendments referred to expert advisory committee

Subdivision 3D.2 of the *Therapeutic Goods Regulations 1990* (the Regulations) sets out the procedure to be followed where the Secretary receives an application under section 52EAA of the *Therapeutic Goods Act 1989* (the Act) to amend the current Poisons Standard or decides to amend the Poisons Standard on his or her own initiative and decides to refer the proposed amendment to an expert advisory committee. These include, under regulation 42ZCZK, that the Secretary publish (in a manner the Secretary considers appropriate) the proposed amendment to be referred to an expert advisory committee, the committee to which the proposed amendment will be referred, and the date of the committee meeting. The Secretary must also invite public submissions to be made to the expert advisory committee by a date mentioned in the notice as the closing date, allowing at least 20 business days after publication of the notice.

In accordance with regulation 42ZCZK of the Regulations, the Secretary invites public submissions on scheduling proposals referred to the June 2021 meeting of the Joint Advisory Committee on Medicines and Chemicals Scheduling (Joint ACMS-ACCS #28). Submissions must be received by close of business **7 October 2021**.

1 Proposed amendments referred for scheduling advice to ACMS #35

1.1 Astodrimer sodium

Proposal

The applicant has proposed amendment of 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.

CAS Number:

676271-69-5

Alternative names

2,6-Bis-{(1-napthalenyl-3,6-disulfonic acid)-oxyacetamido}-2,6-bis-2,6-bis-2,6-bis-(2,6-diamino-hexanoylamino)-2,6-diamino-hexanoic acid (diphenylmethyl)-amide, polysodium salt; SPL7013

Applicant

Private applicant

Current scheduling

Astodrimer sodium is currently listed in Schedule 3 of the Poisons Standard:

Schedule 3

ASTODRIMER SODIUM **except** in a condom lubricant.

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ASTODRIMER SODIUM

Schedule 3
Appendix F, Part 3
Appendix H

It is also included under the entries for ASTODRIMER SODIUM in Appendix F and Appendix H as follows:

Appendix F, Part 3

WARNING STATEMENTS

63	See a doctor if you are pregnant or diabetic.
64	See a doctor (or) (dentist) if no better after (Insert number of days as per approved Product Information) days.

69	If symptoms recur within two weeks of completing the course, consult a doctor.
75	Do not use for more than 7 days unless a doctor has told you to.
109	See your healthcare provider if you consider that you may be at risk of a Sexually Transmitted Infection (STI).
110	See a doctor if you plan to become pregnant, or are breastfeeding or plan to breastfeed.

Appendix H

ASTODRIMER SODIUM for the treatment and relief of bacterial vaginosis.

Proposed scheduling

Schedule 3

ASTODRIMER SODIUM **except** in a condom lubricant.

Appendix F, Part 1 – New Entries

113.	Discuss longer periods of use (>2 weeks) with a healthcare provider.
114.	Do not use for more than 16 weeks unless a doctor has told you to.

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, 109, 110, 113, 114	

Appendix H – Amend Entry

ASTODRIMER SODIUM ~~for the treatment and relief of bacterial vaginosis.~~

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ASTODRIMER SODIUM

Schedule 3
Appendix F, Part 3
Appendix H

Key uses / expected use

Therapeutic goods, including medical devices

Application summary - reasons for proposal

- Astodrimer sodium is currently formulated in a vaginal gel Class IIa medical device that is included on the ARTG, for use in the treatment, relief and prevention of bacterial vaginosis (BV). The indications were recently updated to include the prevention of recurrent BV.
- The applicant proposes that the existing Appendix F and Appendix H entries for astodrimer sodium be updated to accommodate the new broader indication for the vaginal gel, including prevention of BV. The amendments would allow advertising of astodrimer for any indication and create new label warning statements for preventative use.
- The requested amendments to the Poisons Standard related to astodrimer sodium are intended to enable the risks and potential benefits of a non-antibiotic vaginal gel for the prevention of recurrent BV, to be communicated to Australian women through labelling and consumer advertising.
- The applicant notes that:
  - For the majority of women BV is not serious, however the psychological impact on those with the condition can be significant and reports indicate that it is twice as common as vaginal candidiasis. Many women may not seek treatment from a physician due to the embarrassment caused by their symptoms.
  - It is common for BV to recur after treatment, and it is estimated that more than half of women who are treated for the condition will experience a recurrence within three months. Recurrent BV is associated with mental health and psychosocial issues such as feeling of depression, increased anxiety and shame, which can impact on the sufferer's professional and personal relationships.
  - Antibiotics are a common treatment for symptomatic BV, however the associated side effects and potential for the development of antibiotic resistance make the repeated and prolonged use of this class of medicines unacceptable.
  - Astodrimer sodium is also formulated in a condom lubricant, an application which is currently exempt from scheduling in the Poisons Standard.
  - Due to the molecule's physical size and negative charge, astodrimer sodium is not absorbed into the bloodstream following topical application to mucosal epithelial surfaces. This translates to minimal systemic exposure and toxicity following repeat dosing in all species studied in in safety and tolerability testing. The substance does not represent a genetic, carcinogenic or reproductive risk.

Australian regulations

- According to the TGA Ingredient Database,[1] astodrimer sodium is:
  - Available for use as an Active Ingredient in Devices.

[1] TGA Ingredient Database https://www.ebs.tga.gov.au/

  - Available for use as an Excipient in Devices.
  - Not available as an Equivalent Ingredient in any application.

- As of August 2021, there were two devices currently active on the Australian Register of Therapeutic Goods (ARTG)[2] that include astodrimer sodium: a medicated latex condom and a vaginal gel.
- Astodrimer sodium is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[3] No.1 of 2021.
- Astodrimer sodium is not included in the TGA prescribing medicines in pregnancy database[4].
- There are no warning statements pertaining to astodrimer sodium in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[5].
- As of August 2021, there were no reports of adverse events for products containing astodrimer sodium as an active ingredient on the Database of Adverse Event Notifications (DAEN).[6]
- As of August 2021, there were no products containing astodrimer sodium listed on the Public Chemical Registration Information System Search (PubCRIS).[7]

International regulations

- Astodrimer sodium is not included in the Health Canada drug product database[8], the United States Food and Drug Administration's approved drug products database[9], the New Zealand Inventory of Chemicals[10], the New Zealand (Medsafe) medicines classification database[11], the European Commission database for information on cosmetic substances and ingredients[12], or Ireland's Health Products Regulatory Authority medicines database[13].

1.2 Flurbiprofen

Proposal

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

[2] ARTG database https://www.tga.gov.au/artg
[3] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[4] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[5] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[6] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[7] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[8] Health Canada www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
[9] FDA www.accessdata.fda.gov/scripts/cder/daf/
[10] NZIoC www.epa.govt.nz/database-search/new-zealand-inventory-of-chemicals-nzioc/
[11] Medsafe www.medsafe.govt.nz/profs/class/classintro.asp
[12] CosIng ec.europa.eu/growth/tools-databases/cosing/index.cfm?fuseaction=search.simple
[13] HPRA www.hpra.ie/

CAS number:

5104-49-4

Alternative names

2-Fluoro-α-methyl[1,1′-biphenyl]-4-acetic acid; 2-(2-fluoro-4-biphenylyl)propionic acid; 3-fluoro-4-phenylhydratropic acid

Applicant

Private applicant

Current scheduling

Flurbiprofen is currently listed in Schedules 2 and 4 of the Poisons Standard as follows:

Schedule 4

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

Schedule 2

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.

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FLURBIPROFEN

Schedule 4
Schedule 2

Proposed scheduling

Schedule 4

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

Schedule 2 – Amend Entry

FLURBIPROFEN in preparations for topical oral use when:

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

   i) 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

Application summary - reasons for proposal

- The application seeks the scheduling exemption of undivided flurbiprofen preparations containing 0.25 per cent or less or 10 mg per dose or less of flurbiprofen, that are labelled for the treatment of adults over 18 years of age in a primary pack containing not more than 15 millilitres. The proposed changes would move flurbiprofen throat sprays from Schedule 2 to unscheduled medicines, which would allow these products to be sold in general retail outlets such as supermarkets.
- The applicant notes:
  - Flurbiprofen throat spray is used for the relief of pain, swelling and inflammation associated with sore throats. The spray is intended to treat the affected region while minimising systemic exposure.
  - Flurbiprofen is an established non-steroidal anti-inflammatory drug (NSAID) of the propionic acid group which also includes ibuprofen.
  - In humans flurbiprofen has potent analgesic, antipyretic, and anti-inflammatory properties. It is available in a number of formulations, including lozenges, metered dose aerosols (throat sprays), eye drops and oral tablets (overseas).
  - Throat sprays tend to be used in situations where consumers are seeking rapid pain relief or to relieve more severe throat pain. As severe throat pain commonly occurs at night[14], a throat spray is likely to be a preferred dosage format as it allows rapid application and pain relief, without the need to stay awake whilst sucking on a lozenge.
  - There is a consumer need and benefit for increased access to this dosage formulation outside of normal pharmacy operating hours. As an unscheduled medicine this could be purchased from supermarkets or similar stores which have longer operating hours.
  - A similar application was rejected in 2017, after advice from the ACMS indicated that there was limited benefit to public health from the down-scheduling of these preparations, limited in-market experience with the throat spray, and concerns raised regarding a fatal hypersensitivity reaction to the substance.
  - In June 2020, divided preparations of flurbiprofen were down-scheduled from Schedule 2 to unscheduled, in pack sizes of not more than 16 units when labelled only for the treatment of adults and children over 12 years. The proposed limited pack size

[14] Winkle. Market research, Nurofen® dairy-based pain tracker. 2018

of 15 mL represents 3 days therapy for patients taking the maximum dose of the throat spray (5 doses per day), which is comparable to other unscheduled analgesic options including flurbiprofen lozenges.

Key uses / expected use

Medicines

Australian regulations

- According to the TGA Ingredient Database,[15] flurbiprofen is:
  - Available for use as an Active Ingredient in Biologicals, Export Only, Over the Counter and Prescription Medicines.
  - Available for use as an Excipient Ingredient in Biologicals, Devices and Prescription Medicines.
  - Not available as an Equivalent Ingredient in any application.
- As of August 2021, there were four medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[16] that contain flurbiprofen as an active ingredient. These include one prescription and three non-prescription medicines.
- Flurbiprofen is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[17] No.1 of 2021 .
- The TGA prescribing medicines in pregnancy database[18] classifies flurbiprofen as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
FLURBIPROFEN	C	Ophthalmic drugs		
Category C – Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.				

- The Therapeutic Goods (Medicines Advisory Statements) Specification 2019[19] requires the following warning statements pertaining to flurbiprofen to be included on the labelling:

[15] TGA Ingredient Database https://www.ebs.tga.gov.au/

[16] ARTG database https://www.tga.gov.au/artg

[17] Therapeutic Goods (Permissible Ingredients) Determination
https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination

[18] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database

[19] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213

Substance	Conditions	Required Statement(s)
Flurbiprofen (1 of 2)	In oral preparations that do NOT include indications for use in children under 12 years of age	• Do not use if you have a stomach ulcer. • Do not use if you have impaired kidney function. • Do not use if you have heart failure. • Do not use if you are allergic to flurbiprofen or other anti-inflammatory medicines. • If you get an allergic reaction, stop taking and see your doctor immediately. • Unless a doctor has told you to, do not use if you have asthma. • Unless advised by your doctor or pharmacist, do not use with other products containing flurbiprofen, aspirin or other anti-inflammatory medicines or with medicines that you are taking regularly. • Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage. • Do not use if trying to become pregnant, or during the first 6 months of pregnancy, except on doctor's advice. Do not use at all during the last 3 months of pregnancy.
Flurbiprofen (2 of 2)	In oral preparations that include indications for use in children under 12 years of age	• Do not use if you have a stomach ulcer. • Do not use if you have impaired kidney function. • Do not use if you have heart failure. • Do not use if you are allergic to flurbiprofen or other anti-inflammatory medicines. • If you get an allergic reaction, stop taking and see your doctor immediately. • Unless a doctor has told you to, do not use if you have asthma. • Unless advised by your doctor or pharmacist, do not use with other products containing flurbiprofen, aspirin or other anti-inflammatory medicines or with medicines that you are taking regularly. • Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful and increase the risk of heart attack, stroke or liver damage. • Do not use if trying to become pregnant, or during the first 6 months of pregnancy, except on doctor's advice. Do not use at all during the last 3 months of pregnancy. • Ask your doctor or pharmacist before use of the medicine in children suffering from dehydration through diarrhoea and/or vomiting.

- As of August 2021, there were six reports of adverse events for products containing flurbiprofen as an active ingredient on the Database of Adverse Event Notifications (DAEN)[20] with five reports where flurbiprofen was the single suspected medicine. There were no reports of deaths associated with flurbiprofen use.
- As of August 2021, there were no products containing flurbiprofen as an active ingredient/constituent or scheduled substance listed on the Public Chemical Registration Information System Search (PubCRIS).[21]

International regulations

As of August 2021:

- Flurbiprofen is not included in the WHO Model List of Essential Medicines 2019[22].
- The Health Products Regulatory Authority of Ireland[23] regulates flurbiprofen as an over-the-counter medicine supplied through pharmacies only.
- The United States Food and Drug Administration Approved Drug Products database (Drugs@FDA)[24] approves the use of flurbiprofen oral tablets and ophthalmic solution/drops as prescription medicines.
- Flurbiprofen oral tablets are approved for use as prescription medicines according to the Canadian (Health Canada) Drug Product Database[25].
- In the UK (as referred to in the Electronic Medicines Compendium[26]) flurbiprofen oral tablets and eye drops are prescription only medicines and lozenges are pharmacy medicines.
- According to the New Zealand Medicines and Medical Devices Safety Authority (MedSafe)[27] flurbiprofen is available as follows:

Ingredient	Conditions	Classification
Flurbiprofen	**except** in locally acting oromucosal preparations containing 10 milligrams or less per dosage unit	Prescription
Flurbiprofen	in locally acting oromucosal preparations containing 10 milligrams or less per dosage unit	Pharmacy Only

[20] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[21] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[22] WHO model list of essential medicines – 21st list, 2019 www.who.int/publications/i/item/WHOMVPEMPIAU2019.06
[23] Health Products Regulatory Authority (HPRA) https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=&field=
[24] FDA Approved Drug Products Database https://www.accessdata.fda.gov/scripts/cder/daf/
[25] Canadian (Health Canada) Drug Product Database https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[26] Electronic Medicines Compendium https://www.medicines.org.uk/emc/
[27] New Zealand Medicines and Medical Devices Safety Authority (MedSafe) https://www.medsafe.govt.nz/profs/class/classintro.asp

2 Proposed amendments referred for scheduling advice to ACCS #32

2.1 Chromates and chromium trioxide

Proposal

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

CAS Number:

24613-89-6 (dichromium tris (chromate))

7789-06-2 (strontium chromate)

1333-82-0 (chromium trioxide)

7738-94-5 (chromic acid)

Applicant

Private

Current scheduling

Chromates are listed in Schedule 6 of the current Poisons Standard as follows:

> **Schedule 6**
>
> CHROMATES (including dichromates) **except** in paints or tinters containing 5 per cent or less of chromium as the ammonium, barium, calcium, iron, potassium, sodium, strontium or zinc chromate calculated on the non-volatile content of the paint or tinter.
>
> **Index**
>
> **CHROMATES**
> cross reference: AMMONIUM CHROMATE, BARIUM CHROMATE, CHROMIUM, COPPER-CHROME-ARSENIC, DICHROMATES, POTASSIUM CHROMATE, ZINC CHROMATE, SODIUM CHROMATE, STRONTIUM CHROMATE
>
> Schedule 6
> Appendix E, Part 2
> Appendix F, Part 3

It is also included under the entry CHROMATES in Appendices E and F as follows:

> **Appendix E, Part 2**
>
> **STANDARD STATEMENTS**
>
> **Basic**

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

General

G3	If swallowed, do NOT induce vomiting.

Eyes

E2	If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.

Skin

S1	If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

Appendix F, Part 3

SAFETY DIRECTIONS

1	Avoid contact with eyes.
4	Avoid contact with skin.
8	Avoid breathing dust (or) vapour (or) spray mist.

Chromium trioxide is listed in Schedule 6 of the current Poisons Standard as follows:

Schedule 6

CHROMIUM TRIOXIDE (excluding its salts and derivatives)

Index

CHROMIUM TRIOXIDE

Schedule 6

It is also included under the entry CHROMIUM TRIOXIDE in Appendices E and F as follows:

Appendix E, Part 2

STANDARD STATEMENTS

Basic

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

General

G3	If swallowed, do NOT induce vomiting.

Eyes

E2	If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.

Skin

S1	If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

Appendix F, Part 3

WARNING STATEMEMTS

2	Corrosive.
14	Dust will irritate and burn eyes, nose and skin.
15	Liquid will cause burns.
23	May cause fire or explosion.

SAFETY DIRECTIONS

1	Avoid contact with eyes.
4	Avoid contact with skin.
8	Avoid breathing dust (or) vapour (or) spray mist.
13	Do not allow product to come into contact with combustible materials such as paper, fabric, sawdust or kerosene.

Proposed scheduling

Schedule 6 – Amend Entries

CHROMATES (including dichromates) **except**:

a) in paints or tinters containing 5 per cent or less of chromium as the ammonium, barium, calcium, iron, potassium, sodium, strontium or zinc chromate calculated on the non-volatile content of the paint or tinter; or

b) in treatment layers of coated metal articles where the proportion of chromates does not exceed 0.1% w/w of the article.

CHROMIUM TRIOXIDE (excluding its salts and derivatives) **except** in treatment layers of coated metal articles where the proportion of chromates does not exceed 0.1% w/w of the article.

The proposal does not include any changes to the existing entries for these substances in Appendix E, Appendix F or the index.

Key uses / expected use

Industrial use

Application summary - reasons for proposal

- Chromium (VI) compounds are used in the treatment layers of pre-painted metal articles. These treatment layers do not currently meet the exception under the Schedule 6 entry for chromates. The treatment layers are very thin, and the resulting proportion of chromates is less than 0.1% w/w of the article.
- In galvanised metal articles chromium (VI) compounds are reacted to form a conversion coating, which is not considered a 'paint'. This coating is very thin, and the resulting proportion of chromates is less than 0.1% w/w of the article.
- Chromium (VI) compounds in a treatment layer are either subsequently over-coated with paint or are chemically bound to the metal surface during the manufacturing process.
- Substantial levels of chromium (VI) compounds are unlikely to be released from the treatment layer of a coated metal article during the recommended and normal patterns of installation and use. As a result, the exposure of human handlers to chromium (VI) compounds during installation and use is expected to be no greater than that currently allowed for exception to scheduling.
- The proposed threshold value of 0.1% w/w is aligned with both the most sensitive cut-off values for the classification of mixtures under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS 2017) and the European Chemicals Agency Guidance (ECHA) on requirements for substances in articles.
- The current Schedule 6 packaging and labelling requirements are misaligned for coated metal articles.
- The previously considered toxicity of chromium (VI) compounds remains unchanged.

Australian regulations

As of August 2021:

- Chromates and chromium trioxide are not included in the TGA Ingredient Database[28].
- There are no products in the Australian Register of Therapeutic Goods (ARTG)[29] that contain chromium trioxide or the chromates specified in the application.

[28] TGA Ingredient Database https://www.ebs.tga.gov.au/
[29] ARTG database https://www.tga.gov.au/artg

- Chromates and chromium trioxide are not permitted to be included in listed medicines as they are not included in the Therapeutic Goods (Permissible Ingredients) Determination[30] No.1 of 2021.
- Chromates and chromium trioxide are not in the TGA prescribing medicines in pregnancy database[31].
- There are no warning statements pertaining to chromates or chromium trioxide in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[32].
- There were six products containing chromates or chromium trioxide listed on the Public Chemical Registration Information System Search (PubCRIS).[33]
- Between 2015-2020 there were no adverse experiences recorded for chromates or chromium trioxide in the APVMA Adverse Experience Reporting Program database (AERP)[34]
- Chromium trioxide, sodium dichromate, potassium chromate and dichromate are included on the Active constituents exempt from the requirements of APVMA approval for use in agricultural or veterinary chemical products.[35]
- Chromium (VI) compounds are included in the AICIS List of chemicals with high hazards for categorisation.[36]
- All relevant compounds are existing chemicals on the Australian Inventory of Industrial Chemicals[37].
- The Australian Drinking Water Guidelines (ADWG)[38] specifies a threshold limit of 0.05mg/L total chromium in drinking water.
- There are two Australian Standards for the coated metal articles used in building trades:
  - AS/NZS 2728:2013 Pre-finished/pre-painted sheet metal products for interior/exterior building applications - Performance requirements.
  - AS1397:2011 - Minimum requirements for continuous hot-dip metallic coated steel sheet and strip.

International regulations

As of August 2021, chromates or chromium trioxide are:

[30] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination

[31] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database

[32] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213

[33] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris

[34] APVMA Adverse Experience Reporting Program database (AERP) https://apvma.gov.au/node/10946

[35] APVMA Active constituents exempt from the requirements of APVMA approval for use in agricultural or veterinary chemical products https://apvma.gov.au/node/4176#C

[36] AICIS List of chemicals with high hazards for categorisation https://www.industrialchemicals.gov.au/help-and-guides/list-chemicals-high-hazards-categorisation

[37] Australian Industrial Chemicals Introduction Scheme – industrial chemicals inventory https://www.industrialchemicals.gov.au/search-inventory

[38] Australian Drinking Water Guidelines https://www.nhmrc.gov.au/about-us/publications/australian-drinking-water-guidelines

- Included in the United States Environmental Protection Agency's (US EPA) Office of Pesticides Programs[39] database, European Commission database for information on cosmetic substances and ingredients database[40] and New Zealand Inventory of Chemicals (NZIoC)[41].
- Included in the European Chemicals Agency (ECHA)[42] database and have the following properties which are of concern: carcinogenic, skin sensitising, mutagenic, respiratory sensitising and suspected to be toxic to reproduction.
- Specifically included in the Canadian (Health Canada) Drug Product Database[43], however all products are listed as "cancelled post-market".

[39] United States Environmental Protection Agency's (US EPA) Office of Pesticides Programs https://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:1:

[40] European Commission database for information on cosmetic substances and ingredients database https://ec.europa.eu/growth/tools-databases/cosing/

[41] New Zealand Inventory of Chemicals (NZIoC) https://www.epa.govt.nz/database-search/new-zealand-inventory-of-chemicals

[42] European Chemicals Agency (ECHA) https://echa.europa.eu/search-for-chemicals

[43] Canadian (Health Canada) Drug Product Database https://health-products.canada.ca/dpd-bdpp/index-eng.jsp

3 Proposed amendments referred for scheduling advice to the Joint ACMS-ACCS #29

3.1 Cis-jasmone

Proposal

The applicant proposes to create new entries in Schedule 5 and Schedule 6 for cis-jasmone for agricultural use.

CAS Number:

488-10-8

Alternative names

3-Methyl-2-(2*Z*)-2-penten-1-yl-2-cyclopenten-1-one

Applicant

Australian Pesticides and Veterinary Medicines Authority (APVMA)

Current scheduling

Cis-jasmone is not specifically scheduled in the current Poisons Standard.

Proposed scheduling

Schedule 6 – New Entry

CIS-JASMONE for agricultural use, **except** when included in Schedule 5.

Schedule 5 – New Entry

CIS-JASMONE for agricultural use, in preparations containing 1.5 per cent or less of cis-jasmone.

Index – New Entry

CIS-JASMONE

Schedule 6
Schedule 5

Key uses / expected use

Agriculture, cosmetic, domestic (e.g. cleaning products, shampoos), food, medicines, medical devices

Application summary - reasons for proposal

- Cis-jasmone is a new agricultural technical grade active constituent (TGAC) in Australia and will require scheduling for the purposes of its approval and future registration in pesticide products.
- Recently cis-jasmone has been used in plant-protection, where it purportedly acts as a repellent to various types of insects through its activity as a biological pesticide. Scheduling of cis-jasmone would offer a promising addition to insect pest management strategies to try to combat the development of insect resistance from repeated use of synthetic chemical insecticides.
- Cis-jasmone is a member of the alicyclic ketone chemical class and is found naturally in a range of edible plants. The highest concentration is found in the jasmine plant (*Jasminum polyanthum*) and is responsible for its characteristic smell.
- Cis-jasmone is currently used in perfumes, cosmetics, personal and household cleaning products, and as a flavouring ingredient in food. Jasmine oil holds a status of "generally recognised as safe" (GRAS) according to the United States Food and Drug Administration.
- Toxicity data relating to the substance indicates that it possesses low acute oral, dermal and inhalational toxicity, but is a moderate eye irritant and slight skin irritant. It may also be an aspiration hazard and potential respiratory irritant. The same presumption of 'toxicological safety' as a food additive does not apply to its pesticidal use.
- Cis-jasmone is not considered to be mutagenic, carcinogenic or to have any genotoxic potential. Based on the moderate eye irritation associated with exposure to the substance, the toxicity profile is considered to be consistent with the Schedule 6 classification. A Schedule 5 entry for low concentrations can be justified by the estimated acute toxicity.

Australian regulations

- According to the TGA Ingredient Database,[44] cis-jasmone is:
  - Available for use as an Active Ingredient in Biologicals and Prescription Medicines.
  - Available for use as an Excipient Ingredient in Biologicals, Devices, Listed Medicines, Over the Counter and Prescription Medicines.
  - Not available as an Equivalent Ingredient in any application.
- As of August 2021, there were no medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[45] that contain cis-jasmone as an active ingredient. There were 51 prescription medicines, 20 non-prescription medicines, 24 listed medicines and two devices that contain cis-jasmone as an excipient or other ingredient.

[44] TGA Ingredient Database https://www.ebs.tga.gov.au/

[45] ARTG database https://www.tga.gov.au/artg

- According to the Therapeutic Goods (Permissible Ingredients) Determination[46] No.1 of 2021, cis-jasmone is permitted to be included in listed medicines as follows:

Item	Ingredient name	Purpose	Specific requirements
1426	CIS-JASMONE	E	Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance. If used in a flavour the total flavour concentration in a medicine must be no more than 5%. If used in a fragrance the total fragrance concentration in a medicine must be no more than 1%.
E = excipient for a medicine meaning an ingredient that is not an active ingredient or a homoeopathic preparation ingredient			

- Cis-jasmone is not included in the TGA prescribing medicines in pregnancy database[47].
- There are no warning statements pertaining to cis-jasmone in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[48]
- As of August 2021, there were no reports of adverse events for products containing cis-jasmone as an active ingredient on the Database of Adverse Event Notifications (DAEN)[49].
- As of August 2021, there were no products containing cis-jasmone listed on the Public Chemical Registration Information System Search (PubCRIS).[50]

International regulations

- Cis-jasmone is included in the United States Environmental Protection Agency's (US EPA) Office of Pesticides Programs[51] database as "pending registration".
- Cis-jasmone for perfuming is included in the European Commission database for information on cosmetic substances and ingredients (COSIng)[52]

[46] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[47] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[48] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[49] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[50] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[51] United States Environmental Protection Agency's (US EPA) Office of Pesticides Programs https://iaspub.epa.gov/apex/pesticides/f?p=CHEMICALSEARCH:1:
[52] European Commission database for information on cosmetic substances and ingredients database https://ec.europa.eu/growth/tools-databases/cosing/

- Cis-jasmone is included in Health Canada's Pest Management Regulation Agency database[53].
- The substance is not included in the New Zealand Medsafe[54] medicines classification database, the Canadian (Health Canada) Drug Product Database[55], the United States Food and Drug Administration Approved Drug Products Database (Drugs@FDA)[56], New Zealand Inventory of Chemicals (NZIoC)[57], or the EU Pesticides Database[58].
- The European Chemicals Agency (ECHA)[59] has a hazard warning that cis-jasmone causes 'serious eye irritation and causes skin irritation'.

3.2 Cannabis and tetrahydrocannabinols

Proposal

The applicant has proposed amendment of the existing Schedule 8 entries for cannabis and tetrahydrocannabinols to include veterinary use of these substances (except in animals for human consumption).

CAS Number:

Cannabis contains numerous related compounds known as cannabinoids. Cannabinoids specifically detailed in the application include:

1972-08-3 (Delta-9-tetrahydrocannabinol)

25654-31-3 (Cannabigerol)

13956-29-1 (Cannabidiol)

20675-51-8 (Cannabichromene)

521-35-7 (Cannabinol)

21366-63-2 (Cannabicyclol)

52025-76-0 (Cannabielsoin)

11003-36-4 (Cannabitriol)

Alternative names

Marijuana

Applicant

Private applicant

[53] Canada's Pest Management Regulation Agency https://pesticide-registry.canada.ca/en/active-ingredient-search.html
[54] New Zealand Medicines and Medical Devices Safety Authority (MedSafe) https://www.medsafe.govt.nz/profs/class/classintro.asp
[55] Canadian (Health Canada) Drug Product Database https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[56] FDA Approved Drug Products Database https://www.accessdata.fda.gov/scripts/cder/daf/
[57] New Zealand Inventory of Chemicals (NZIoC) https://www.epa.govt.nz/database-search/new-zealand-inventory-of-chemicals-nzioc/DatabaseSearchForm/?SiteDatabaseSearchFilters=36&Keyword=acequinocyl&DatabaseType=NZIOC
[58] European Union Pesticides Database https://ec.europa.eu/food/plants/pesticides/eu-pesticides-database_en
[59] European Chemicals Agency (ECHA) https://echa.europa.eu/search-for-chemicals

Current scheduling

Cannabis and tetrahydrocannabinols are currently in Schedule 8 and Schedule 9 of the Poisons Standard as follows:

Schedule 9

CANNABIS (including seeds, extracts, resins, and the plant and any part of the plant when packed or prepared), **except**:

a) when separately specified in these Schedules; or

b) processed hemp fibre containing 0.1 per cent or less of tetrahydrocannabinols and hemp fibre products manufactured from such fibre; or

c) when in hemp seed oil for purposes other than internal human use containing 50 mg/kg or less of cannabinoids, including 20 mg/kg or less of tetrahydrocannabinols, when labelled with either of the following warning statements:

    i) Not for internal use; or

    ii) Not to be taken.

TETRAHYDROCANNABINOLS and their alkyl homologues, **except**:

a) when included in Schedule 4 or Schedule 8; or

b) processed hemp fibre containing 0.1 per cent or less of tetrahydrocannabinols, and hemp fibre products manufactured from such fibre; or

c) in hemp seed oil for purposes other than internal human use containing 50 mg/kg or less of total cannabinoids, including 20 mg/kg or less of tetrahydrocannabinols, when labelled with either of the following warning statements:

    i) Not for internal use; or

    ii) Not to be taken.

Schedule 8

CANNABIS (including seeds, extracts, resins and the plant, and any part of the plant) when prepared or packed for human therapeutic use, when:

a) cultivated or produced, or in products manufactured[1], in accordance with the *Narcotic Drugs Act 1967*; and/or

b) for use in products manufactured in accordance with the *Narcotic Drugs Act 1967*; and/or

c) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the *Therapeutic Goods Act 1989*; and/or

d) in therapeutic goods supplied in accordance with the *Therapeutic Goods Act 1989*,

    except when:

    i) it is in a product to which item 4, 8, 10, 11 or 12 of Schedule 5A to the *Therapeutic Goods Regulations 1990* applies; or

    ii) separately specified in the NABIXIMOLS entry in this Schedule; or

iii) captured by the CANNABIDIOL entry in Schedule 4 or Schedule 3.

TETRAHYDROCANNABINOLS when extracted from cannabis for human therapeutic use, when:

a) included in products manufactured in accordance with the Narcotic Drugs Act 1967; and/or

b) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the Therapeutic Goods Act 1989; and/or

c) in therapeutic goods supplied in accordance with the Therapeutic Goods Act 1989,

except when:

i) it is in a product to which item 4, 8, 10, 11 or 12 of Schedule 5A to the Therapeutic Goods Regulations 1990 applies; or

ii) separately specified in the NABIXIMOLS entry in this Schedule; or

iii) captured by the CANNABIDIOL entry in Schedule 4 or Schedule 3.

CANNABIS and TETRAHYDROCANNABINOLS are also included in **Appendix D** of the Poisons Standard as follows:

1. Poisons available only from or on the prescription or order of an authorised medical practitioner:

   CANNABIS for human use.

   TETRAHYDROCANNABINOLS for human use.

Proposed scheduling

The applicant is not seeking amendment to the Schedule 9 entries for cannabis or tetrahydrocannabinols.

Schedule 8 – Amend Entry

CANNABIS (including seeds, extracts, resins and the plant, and any part of the plant) when prepared or packed for human or animal therapeutic use, when:

a) cultivated or produced, or in products manufactured[1], in accordance with the *Narcotic Drugs Act 1967*; and/or

b) for use in products manufactured in accordance with the *Narcotic Drugs Act 1967*; and/or

c) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the *Therapeutic Goods Act 1989*; and/or

d) in therapeutic goods supplied in accordance with the *Therapeutic Goods Act 1989*,

except when:

i) it is in a product to which item 4, 8, 10, 11 or 12 of Schedule 5A to the *Therapeutic Goods Regulations 1990* applies; or

ii) separately specified in the NABIXIMOLS entry in this Schedule; or

iii) captured by the CANNABIDIOL entry in Schedule 4 or Schedule 3; or

iv) it is intended to be used on animals bred for human consumption.

TETRAHYDROCANNABINOLS when extracted from cannabis for human or animal therapeutic use, when:

a) included in products manufactured in accordance with the Narcotic Drugs Act 1967; and/or

b) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the Therapeutic Goods Act 1989; and/or

c) in therapeutic goods supplied in accordance with the Therapeutic Goods Act 1989,

except when:

i) it is in a product to which item 4, 8, 10, 11 or 12 of Schedule 5A to the Therapeutic Goods Regulations 1990 applies; or

ii) separately specified in the NABIXIMOLS entry in this Schedule; or

iii) captured by the CANNABIDIOL entry in Schedule 4 or Schedule 3; or

iv) intended to be used on animals bred for human consumption.

Appendix D – Amend Entry

1. Poisons available only from or on the prescription or order of an authorised medical practitioner:

~~CANNABIS for human use.~~

~~TETRAHYDROCANNABINOLS for human use.~~

5. Poisons for which possession without authority is illegal (e.g. possession other than in accordance with a legal prescription).

CANNABIS for human use.

TETRAHYDROCANNABINOLS for human use.

Key uses / expected use

Medicines

Application summary - reasons for proposal

- Veterinarians currently only have access to S4 medicinal cannabis medicines via compounded formulations, “off-label” use in individual animals, or special consent to import an unregistered veterinary product. Vets have no access to cannabis or cannabis-related medicines under the existing S3, S8 and S9 entries for these substances. The applicant is seeking changes that would allow use of cannabis under the S8 entry for therapeutic use in animals.
- There has been a recent increase in animal research and real-world evidence. Rewording the S8 schedule of medicinal cannabis to include “therapeutic use in animals” will increase access and provide treatment option to veterinarians that are not presently available. This will benefit both humans and other animals.

- The same or similar therapeutic benefits experienced by humans are applicable for other animals, including those for products containing tetrahydrocannabinol (THC). Some of the possible indications for cannabinoid therapy in animals include pain relief, treatment of inflammation, treatment of cancers, treatment of anxiety and stress, treatment of epilepsy, appetite stimulant and as antioxidants and neuroprotectants.
- The endocannabinoid system (ECS) has been identified in nearly all animals (including humans), from complex mammals like primates to phylogenetically primitive animals such as the cnidarians[60] . The near universal presence and early emergence of the ECS, evolutionarily, is a strong indicator of its biological importance. Cannabinoid receptors are expressed in most animals, including vertebrates (mammals, birds, reptiles, and fish) and invertebrates.
- The current wording impacts animal welfare in two ways. Firstly, animals do not have legal access to these new therapeutic tools that can provide improved outcomes and enhanced care for particular indications. Secondly, as public awareness of the benefits of medicinal cannabis grows, owners of animals are using illicit products without veterinary support, advice and control; potentially endangering the welfare of their animals.
- Accessing cannabis products through veterinarians offers benefits to veterinary healthcare professionals, their clients and their patients. In many countries such as Chile, Uruguay, Peru, Columbia and Mexico, veterinarians are allowed to prescribe cannabis to animals, and others like Canada and Brazil are currently considering applications to legislate the prescription of cannabis to animals.
- Due to the prolonged elimination time for many cannabinoids and the illicit nature of these substances in some settings, it is proposed to exclude "animals intended for human consumption" from the Schedule 8 entry; this treatment would be captured by the Schedule 9 entry.

Australian regulations

- According to the TGA Ingredient Database,[61] cannabis sativa is:
  - Available for use as an Active Ingredient in Export Only and Prescription Medicines;
  - Not available as an Excipient Ingredient in any application;
  - Not available as an Equivalent Ingredient in any application.
- Cannabidiol is also available for use in Over the Counter medicines, in addition to Export Only and Prescription medicines.
- As of August 2021, there were 8 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[62] that only contain cannabis sativa as an active ingredient. All products are listed for export only. In addition, there are two registered products available on the Australian market that contain cannabinoids as active ingredients: an oral liquid containing cannabidiol, and an oromucosal spray containing nabiximols.

[60] Hartsel, J.A., Boyar, K., Pham, A., Silver, R.J. and Makriyannis, A., 2019. Cannabis in veterinary medicine: cannabinoid therapies for animals. In Nutraceuticals in Veterinary Medicine (pp. 121- 155). Springer, Cham.

[61] TGA Ingredient Database https://www.ebs.tga.gov.au/

[62] ARTG database https://www.tga.gov.au/artg

- As of August 2021 cannabis and tetrahydrocannabinols are not permitted to be included in listed medicines as they are not included in the Therapeutic Goods (Permissible Ingredients) Determination[63] No. 1 of 2021.
- Cannabis and tetrahydrocannabinols is not included in the TGA prescribing medicines in pregnancy database[64].
- There are no warning statements pertaining to cannabis and tetrahydrocannabinols in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[65]
- As of August 2021, there were 61 reports of adverse events for products containing cannabis and/or cannabinoids as an active ingredient on the Database of Adverse Event Notifications (DAEN),[66] with 51 reports where cannabis or a related substance was the single suspected medicine.
- As of August 2021, there were no products containing cannabis and/or tetrahydrocannabinols listed on the Public Chemical Registration Information System Search (PubCRIS).[67]
- Therapeutic Goods (Standard for Medicinal Cannabis) (TGO93) Order 2017.

International regulations

- United States Food and Drug Administration Approved Drug Products Database (Drugs@FDA)[68] regulate cannabidiol as a prescription only medicine.
- Cannabis and tetrahydrocannabinols are not included in the WHO Model List of Essential Medicines 2019.[69]
- The Health Products Regulatory Authority of Ireland[70] regulates Delta-9-tetrahydrocannabinol as a prescription-only medicine.
- Cannabinol and Delta-9-tetrahydrocannabinol are approved for use as prescription-only human medicines in Canada, according to the Canadian (Health Canada) Drug Product Database.[71]
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe),[72] Cannabis sativa is a Class C1 Controlled Drug in New Zealand.

[63] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination

[64] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database

[65] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213

[66] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx

[67] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris

[68] FDA Approved Drug Products Database https://www.accessdata.fda.gov/scripts/cder/daf/

[69] WHO Model List of Essential Medicines 2019: https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06

[70] Health Products Regulatory Authority of Ireland: https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/

[71] Canadian (Health Canada) Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp

[72] New Zealand Medicines and Medical Devices Safety Authority (Medsafe): https://www.medsafe.govt.nz/profs/class/classintro.asp

3.3 Meloxicam

Proposal

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

CAS Number:

71125-38-7

Alternative names

4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide

Applicant

Australian Pesticides and Veterinary Medicines Authority (APVMA)

Current scheduling

Meloxicam is currently listed in Schedule 4 of the Poisons Standard:

Schedule 4

MELOXICAM.

Index

MELOXICAM

Schedule 4

Proposed scheduling

Schedule 6 – New Entry

MELOXICAM in injectable preparations containing 2 per cent or less of meloxicam for the pre-surgical treatment of sheep prior to castration, tail docking, and mulesing.

Schedule 4 – Amend Entry

MELOXICAM **except** when included in Schedule 6.

Index – Amend Entry

MELOXICAM

Schedule 6
Schedule 4

Key uses / expected use

Medicines, veterinary, agriculture

Application summary - reasons for proposal

- Meloxicam is used as an anti-inflammatory, anti-endotoxic, anti-exudative, analgesic and antipyretic in a number of veterinary products. These are all currently captured in Schedule 4 of the Poisons Standard.
- This application relates to a product containing meloxicam in an injection formulation indicated to alleviate pain and inflammation in sheep, associated with the routine husbandry procedures of castration, tail docking and mulesing. The proposed Schedule 6 entry would allow for the product to be administered by farmers.
- Animal welfare guidelines mandate pain relief in sheep undergoing painful mulesing and marking procedures. Such procedures are routinely carried out on farm by trained personnel, without veterinary intervention or supervision.
- Farmers routinely administer other injectable products, including vaccines, and are familiar with safety procedures required for safe administration.
- Meloxicam has a moderate toxicity based on acute oral, intravenous and intraperitoneal studies. The toxicity profile is consistent with a Schedule 6 classification.
- The toxicity, adverse effects, interactions and potential for misuse of the substance can be managed by appropriate labelling – including safety directions, first aid and additional user safety statements.
- The acute oral LD50 in rats (83.5 mg/kg bw/day) of meloxicam is consistent with a Schedule 6 classification, although no data is available on acute inhalation and dermal toxicity, or skin and eye irritation.

Australian regulations

- According to the TGA Ingredient Database,[73] meloxicam is:
  - available for use as an active ingredient in biologicals, export only and prescription medicines;
  - available for use as an excipient ingredient in biologicals, devices and prescription medicines; and
  - not available as an equivalent ingredient in any application.
- As of August 2021, there were 71 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[74] that contain meloxicam as an active ingredient. These include 70 prescription medicines and one export only medicine.
- Meloxicam is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[75] No.1 of 2021.

[73] TGA Ingredient Database https://www.ebs.tga.gov.au/

[74] ARTG database https://www.tga.gov.au/artg

[75] Therapeutic Goods (Permissible Ingredients) Determination:
https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination

- The TGA prescribing medicines in pregnancy database[76] classifies meloxicam as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Meloxicam	C	Musculoskeletal System	Non-steroidal anti-inflammatory drugs (NSAIDS)	
Category C – Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.				

- There are no warning statements pertaining to meloxicam in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[77]
- In May 2011 – May 2021, there were 251 reports of adverse events for products containing meloxicam as an active ingredient on the Database of Adverse Event Notifications (DAEN),[78] with 148 reports where meloxicam was the single suspected medicine.
- As of August 2021, there were 56 products containing meloxicam listed on the Public Chemical Registration Information System Search (PubCRIS).[79]
- In 2015 – 2020, the following adverse experiences were recorded for meloxicam in the APVMA Adverse Experience Reporting Program database (AERP):[80]
  - 74 reports of serious incidents classified as related to animal health; and
  - 1 report of a serious incident classified as related to efficacy.

International regulations

- Meloxicam is not included in the WHO Model List of Essential Medicines 2019.[81]
- The Health Products Regulatory Authority of Ireland[82] regulates meloxicam as a prescription-only medicine.
- The United States Food and Drug Administration[83] approve the use of meloxicam as a prescription-only medicine in the United States.
- Meloxicam is approved for use as a prescription-only human and veterinary medicine in Canada, according to the Canadian (Health Canada) Drug Product Database.[84]

[76] TGA prescribing medicines in pregnancy database: https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[77] Therapeutic Goods (Medicines Advisory Statements) Specification 2019: https://www.legislation.gov.au/Details/F2019L00213
[78] Database of Adverse Event Notifications (DAEN): https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[79] Public Chemical Registration Information System Search (PubCRIS): https://portal.apvma.gov.au/pubcris
[80] APVMA Adverse Experience Reporting Program: database (AERP) https://apvma.gov.au/node/10946
[81] WHO Model List of Essential Medicines 2019: https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06
[82] Health Products Regulatory Authority of Ireland: https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/
[83] United States Food and Drug Administration: https://www.accessdata.fda.gov/scripts/cder/daf/
[84] Canadian (Health Canada) Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp

- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe),[85] meloxicam is available as a prescription-only medicine in New Zealand.

3.4 Choline salicylate

Proposal

The applicant has proposed a new Schedule 3 entry for choline salicylate for human therapeutic or cosmetic use. 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 currently unscheduled.

CAS Number:

2016-36-6

Alternative names

(2-hydroxyethyl)trimethylammonium salicylate; 2-hydroxy-*N*,*N*,*N*-trimethylethanaminium salt with 2-hydroxybenzoic acid (1:1); choline salicylic acid salt; salicylic acid choline salt

Applicant

Private

Current scheduling

Choline salicylate is not specifically scheduled in the current Poisons Standard but is captured as a derivative of salicylic acid. Salicylic acid is listed in Schedule 3 of the Poisons Standard:

> **Schedule 3**
>
> SALICYLIC ACID in preparations for dermal use **except** in preparations containing 40 per cent or less of salicylic acid.

Proposed scheduling

> **Schedule 3 – New Entry**
>
> CHOLINE SALICYLATE for human therapeutic or cosmetic use.
>
> **Index - New Entry**
>
> **CHOLINE SALICYLATE**
>
> Schedule 3

Key uses / expected use

Medicines, cosmetic

[85] New Zealand Medicines and Medical Devices Safety Authority (Medsafe): https://www.medsafe.govt.nz/profs/class/classintro.asp

Application summary - reasons for proposal

- Currently choline salicylate for oromucosal use is unscheduled with no restrictions on purchase. Choline salicylate gels are currently listed and used in Australia for management of pain and swelling associated with teething and mouth ulcers. They are available for purchase without restriction in concentrations of 40% or less. This poses the risk of toxicity particularly due to extended use of teething products containing the substance in infants.
- Choline salicylate is the choline salt of salicylic acid. It is used to relieve mild to moderate pain, reduce fever and inflammation or swelling.
- Choline salicylate relieves pain by inhibition of prostaglandin synthesis and reduces fever by acting on the hypothalamus heat-regulating centre. In oral formulations it is absorbed across the buccal mucosa and is typically used for the treatment of pain and inflammation associated with teething and mouth ulcers.
- Salicylate toxicity is expected with acute exposures of greater than 201mg/kg or chronic exposures of greater than 134mg/kg/day of choline salicylate.
- Exposures of less than 201mg/kg can produce mild salicylate toxicity including nausea, vomiting, epigastric pain. Exposures between 201-402mg/kg can cause moderate toxicity including nausea, vomiting, epigastric pain, tinnitus, tachypnoea, and respiratory alkalosis.
- Exposures of greater than 402mg/kg can produce severe toxicity confusion, altered conscious state, coma, seizures, mixed respiratory acidosis and metabolic acidosis, and are potentially fatal.
- Published cases of salicylate toxicity demonstrate the risks associated with these products, which are not consistent with the scheduling factors for Schedule 2. The current labelling requirements have not been sufficient to prevent poisoning incidents, and self-selection in a pharmacy does not guarantee safe use of the medicine.
- Therapeutic guidelines in Australia do not recommend teething gels because of the lack of evidence of efficacy and the potential for harm[86].
- The proposed change to schedule 3 would ensure continued access to choline salicylate products to the public but with appropriate information provided by pharmacists on indications, maximum dosages, and duration of use, to minimise risk of salicylate toxicity, adverse reactions as well as advice on non-medical management of teething.

Australian regulations

- According to the TGA Ingredient Database,[87] choline salicylate is:
  - Available for use as an Active Ingredient in Biologicals, Export Only, Over the Counter and Prescription Medicines.
  - Available for use as an Excipient Ingredient in Biologicals, Devices and Prescription Medicines.
  - Not available as an Equivalent Ingredient in any application.

[86] 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

[87] TGA Ingredient Database https://www.ebs.tga.gov.au/

- As of August 2021, there were 8 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[88] that contain choline salicylate as an active ingredient. These include 8 non-prescription medicines (all are gels for teething or the treatment of mouth ulcers).
- Choline salicylate is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[89] No.1 of 2021.
- Choline salicylate is not included in the TGA prescribing medicines in pregnancy database[90].
- The Therapeutic Goods (Medicines Advisory Statements) Specification 2019[91] requires the following warning statements pertaining to choline salicylate to be included on the labelling:

Substance	Conditions	Required Statement(s)
Choline salicylate	In preparations for topical oral use.	Do not exceed the recommended dose. Excessive or prolonged use can be harmful.

- As of August 2021, there were 16 reports of adverse events for products containing choline salicylate as an active ingredient on the Database of Adverse Event Notifications (DAEN),[92] with 14 reports where choline salicylate was the single suspected medicine. There were no reports of deaths associated with choline salicylate use.
- As of August 2021, there were no products containing choline salicylate listed on the Public Chemical Registration Information System Search (PubCRIS).[93]

International regulations

- The New Zealand Medicines and Medical Devices Safety Authority (Medsafe)[94] medicines classification database lists choline salicylate as:
  - prescription medicine in products containing greater than 10% choline salicylate in pack sizes exceeding 15 grams, and
  - for general sale otherwise.
- There are no active products on the Health Canada Drug Product Database[95] that contain choline salicylate. Two choline salicylate products are listed on the database as "cancelled post market".
- Choline salicylate is not included in the United States Food and Drug Administration (US FDA) Approved Drugs Database[96], or the New Zealand Inventory of Chemicals (NZIoC)[97].

[88] ARTG database https://www.tga.gov.au/artg
[89] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[90] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[91] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[92] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[93] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[94] New Zealand Medicines and Medical Devices Safety Authority (MedSafe) https://www.medsafe.govt.nz/profs/class/classintro.asp
[95] Canadian (Health Canada) Drug Product Database https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[96] FDA Approved Drug Products Database https://www.accessdata.fda.gov/scripts/cder/daf/
[97] New Zealand Inventory of Chemicals (NZIoC) https://www.epa.govt.nz/database-search/new-zealand-inventory-of-chemicals-nzioc/DatabaseSearchForm/?SiteDatabaseSearchFilters=36&Keyword=acequinocyl&DatabaseType=NZIOC

- Choline salicylate is included on the European Commission's database for cosmetic substances and ingredients[98].
- The Health Products Regulatory Authority in Ireland[99] has authorised three products containing choline salicylate. Two products are oromucosal gels (8.7% choline salicylate) which can be supplied through non-pharmacy outlets without a prescription, and one ear drops product (20% choline salicylate) which is available by prescription only.

4 How to respond

Submissions must be provided by the closing date of **7 October 2021** through our consultation hub. Any submission about any of the proposals to amend the Poisons Standard will be considered at the next meeting of the Advisory Committee on Medicines Scheduling (ACMS), meeting of the Advisory Committee on Chemicals Scheduling (ACCS), or a joint meeting of these two committees.

5 What will happen

All public submissions will be published on the TGA website at Public submissions on scheduling matters, unless marked confidential or indicated otherwise in the submission coversheet (see Privacy information).

Following consideration of public submissions received before the closing date and advice from the expert advisory committee/s, decisions on the proposed amendments will be published as interim decisions on the TGA website: Scheduling delegate's interim decisions & invitations for further comment in **February 2022**.

[98] European Commission database for information on cosmetic substances and ingredients database
https://ec.europa.eu/growth/tools-databases/cosing/

[99] Health Products Regulatory Authority (HPRA)
https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=&field=