Australian Government
Department of Health
Therapeutic Goods Administration

Consultation: Proposed amendments to the Poisons Standard – ACCS, ACMS and joint ACCS/ACMS meetings, March 2022

30 December 2021

TGA Health Safety Regulation

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1 About this consultation

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 March 2022 meeting of the Advisory Committee on Medicines Scheduling (ACMS #37), Advisory Committee on Chemicals Scheduling (ACCS #33) and Joint Advisory Committee on Medicines and Chemicals Scheduling (Joint ACMS-ACCS #30). Submissions must be received by close of business **31 January 2022**.

Submissions 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 31 January 2022.

We aim to provide documents in an accessible format. If you're having problems using this document, please contact medicines.scheduling@health.gov.au.

2 Proposed amendments referred for scheduling advice to ACMS #37

2.1 Azelastine and fluticasone propionate

Proposal

The applicant has proposed amendments to the existing Schedule 2 entries for azelastine and fluticasone propionate to include details specific to an existing fixed-dose combination (FDC) product containing these two substances. The amended entries would allow access to combination azelastine and fluticasone propionate FDC products of certain dosages from a pharmacy without the requirement of a prescription.

CAS number:

Azelastine: 58581-89-8

Fluticasone propionate: 80474-14-2

Alternative names

Azelastine anhydrous

Fluticasone propionate anhydrous

Applicant

Private applicant

Current scheduling

Azelastine

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

Schedule 4

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

Schedule 2

AZELASTINE:

a) in preparations for nasal use; or

b) in topical eye preparations containing 0.05 per cent or less of azelastine.

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ANTIHISTAMINES
cross reference: ASTEMIZOLE, AZELASTINE, BILASTINE, DESLORATADINE, FEXOFENADINE, LORATADINE, TERFENADINE, CETIRIZINE

Schedule 4
Appendix F, Part 3

AZELASTINE

Schedule 4
Schedule 2

Azelastine is also included under the entry ANTIHISTAMINES in Appendix F, Part 3 as follows:

Poison	Warning statements	Safety direction
ANTIHISTAMINES not separately specified in this Appendix **except:** a) dermal, ocular, parenteral and paediatric preparations; b) oral preparations of astemizole, azelastine, bilastine, desloratadine, fexofenadine, loratadine, terfenadine or cetirizine; c) nasal preparations of azelastine; or d) preparations for the treatment of animals.	39 (This medication may cause drowsiness. If affected do not drive a vehicle or operate machinery. Avoid alcohol.) or 40 (This medication may cause drowsiness and may increase the effects of alcohol. If affected do not drive a motor vehicle or operate machinery.)	

Fluticasone propionate

Schedule 4

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

Schedule 2

FLUTICASONE PROPIONATE (excluding derivatives) in aqueous nasal sprays delivering 50 micrograms or less of fluticasone per actuation when the maximum recommended daily dose is no greater than 400 micrograms, for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

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FLUTICASONE
cross reference: FLUTICASONE PROPIONATE, FLUTICASONE FUROATE

Schedule 4

FLUTICASONE PROPIONATE

Schedule 4
Schedule 2

Proposed scheduling

A request has been made to amend the Poisons Standard as follows:

Azelastine

Schedule 4

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

Schedule 2

AZELASTINE:

a) in preparations for nasal use; or

b) in topical eye preparations containing 0.05 per cent or less of azelastine; or

c) when combined with fluticasone propionate (excluding derivatives) in nasal spray suspension delivering 125 micrograms of azelastine and 50 micrograms or less of fluticasone propionate per actuation when the maximum recommended daily dose is no greater than 500 micrograms for azelastine and 200 micrograms for fluticasone propionate, for the symptomatic treatment of allergic rhinitis and rhino-conjunctivitis for up to 6 months in adults and children 12 years of age and over.

Appendix F

Poison	Warning statements	Safety direction
ANTIHISTAMINES not separately specified in this Appendix **except:** a) dermal, ocular, parenteral and paediatric preparations; b) oral preparations of astemizole, azelastine, bilastine, desloratadine, fexofenadine, loratadine, terfenadine or cetirizine;	39 (This medication may cause drowsiness. If affected do not drive a vehicle or operate machinery. Avoid alcohol.) or 40 (This medication may cause drowsiness and may increase the effects of alcohol. If affected do not drive a motor vehicle or operate machinery.)	

c) nasal preparations of azelastine; or d) preparations for the treatment of animals. e) nasal spray preparations of azelastine when combined with fluticasone propionate		

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AZELASTINE
Cross reference: FLUTICASONE PROPIONATE

Schedule 4
Schedule 2

ANTIHISTAMINES

Cross reference: ASTEMIZOLE, AZELASTINE, AZELASTINE IN COMBINATION WITH FLUTICASONE PROPIONATE, BILASTINE, DESLORATADINE, FEXOFENADINE, LORATADINE, TERFENADINE, CETIRIZINE

Schedule 4
Appendix F, Part 3

Fluticasone propionate

Schedule 4

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

Schedule 2

FLUTICASONE PROPIONATE (excluding derivatives)

a) in aqueous nasal sprays delivering 50 micrograms or less of fluticasone per actuation when the maximum recommended daily dose is no greater than 400 micrograms, for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

b) when combined with azelastine in nasal spray suspension delivering 125 micrograms of azelastine and 50 micrograms or less of fluticasone propionate per actuation when the maximum recommended daily dose is no greater than 500 micrograms for azelastine and 200 micrograms for fluticasone propionate, for the symptomatic treatment of allergic rhinitis and rhino-conjunctivitis for up to 6 months in adults and children 12 years of age and over.

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FLUTICASONE PROPIONATE
Cross reference: AZELASTINE

Schedule 4
Schedule 2

Key uses / expected use

Medicines

Background

Azelastine is an antihistamine primarily used topically as a nasal spray. It is indicated for treatment of seasonal and perennial allergic rhinitis.

Fluticasone is a glucocorticoid widely used as an ingredient in inhalers for the preventative management of asthma, and in topical nasal spray preparations indicated for the prophylaxis and treatment of allergic rhinitis in adults over 18 years of age.

These two substances are used in combination for the treatment of moderate to severe allergic rhinitis and rhino-conjunctivitis in adults and children 12 years and older where use of a combination (intranasal antihistamine and glucocorticoid) is considered appropriate by a medical practitioner.

Fixed-dose combination (FDC) nasal spray products containing both azelastine and fluticasone propionate are currently registered on the Australian Register of Therapeutic Goods (ARTG) as Schedule 4 (Prescription Only) medicines. In contrast, nasal spray products containing azelastine or fluticasone propionate, but not both, are currently registered as Schedule 2 (Pharmacy Only) medicines.

Application summary – reasons for proposal

The application was submitted, following advice and clarification from the Therapeutic Goods Administration (TGA) regarding the current scheduling status of the FDC products, to facilitate down-scheduling of these products to Schedule 2 for certain dosages.

The reasons from the applicant are as follows:

- Azelastine hydrochloride and fluticasone propionate have different modes of action and show synergistic effects in terms of improvement of allergic rhinitis and rhino-conjunctivitis symptoms. The use of the two components when contained in separate Schedule 2 labelled proprietary products is not restricted.
- The safety profile of azelastine and fluticasone propionate in combination relative to azelastine and fluticasone propionate single molecule products supports the inclusion of a combination product in Schedule 2.
- The down-scheduling of azelastine and fluticasone propionate combination products from Prescription Only medicines (Schedule 4) to Pharmacy Medicines (Schedule 2) will enhance consumer access to a superior treatment option and a better treatment continuity.

Australian regulations

- Azelastine and fluticasone propionate in a fixed-dose combination (FDC) for nasal use has been registered as a Schedule 4 medicine in Australia since 2014[1]. According to the TGA Ingredient Database,[2] azelastine is:
  - Available for use as an active ingredient in biologicals, over-the-counter and prescription medicines;
  - Available for use as an excipient ingredient in biologicals, devices, over-the-counter and prescription medicines;
  - Available for use as an equivalent ingredient in biologicals, devices, over-the-counter and prescription medicines
- According to the TGA Ingredient Database,[3] fluticasone propionate is:
  - Available for use as an Active Ingredient in biologicals, export only, over-the-counter, and prescription medicines;
  - Available for use as an excipient ingredient in biologicals, devices, prescription medicines;
  - Not available as an equivalent ingredient in any application.
- As of December 2021 there were 13 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[4] that contain azelastine (as hydrochloride) as an active ingredient. These include five prescription and eight non-prescription medicines.
- As of December 2021 there were 78 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[5] that contain fluticasone propionate as an active ingredient. These include 77 prescription and one non-prescription medicine.
- As of December 2021 there were four medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[6] that contain a fixed dose combination of azelastine (as hydrochloride) and fluticasone propionate as active ingredients. These four products are all prescription only medicines (Schedule 4).
- Azelastine and fluticasone propionate are not permitted to be included in listed medicines as they are not included in the Therapeutic Goods (Permissible Ingredients) Determination[7] No. 3 of 2021.

[1] TGA AusPAR for "Dymista, Dylastine" https://www.tga.gov.au/sites/default/files/auspar-fluticasone-propionate-140724.pdf
[2] TGA Ingredient Database https://www.ebs.tga.gov.au/
[3] TGA Ingredient Database https://www.ebs.tga.gov.au/
[4] ARTG database https://www.tga.gov.au/artg
[5] ARTG database https://www.tga.gov.au/artg
[6] ARTG database https://www.tga.gov.au/artg
[7] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic Goods LBPermissible IngredientsRB Determination

- The TGA prescribing medicines in pregnancy database[8] classifies azelastine and fluticasone propionate as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Azelastine	B3	Allergy and immune system	Antihistamines	
Fluticasone propionate	B3	Respiratory system	Inhalational agents	Preventative aerosols and inhalations
Category B3 – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.				

- The Therapeutic Goods (Medicines Advisory Statements) Specification 2019[9] requires the following warning statements pertaining to azelastine to be included on the labelling of products:

Substance	Conditions	Required Statement(s)
Azelastine	In preparations for topical ophthalmic or nasal administration	• If you are pregnant or breastfeeding, check with your doctor or pharmacist before using this medicine.

- There are no warning statements pertaining to fluticasone propionate in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[10].
- As of December 2021 there were 1202 reports of adverse events for products containing fluticasone propionate as an active ingredient on the Database of Adverse Event Notifications (DAEN)[11]. There were 45 reports of adverse events for products containing azelastine as an active ingredient. These numbers include 17 reports where a fixed-dose combination of azelastine and fluticasone propionate was the single suspected medicine, with no reports of deaths associated with use of the combination products. Adverse reactions were varied and showed no commonality.
- As of December 2021 there were no products containing azelastine or fluticasone propionate as an active ingredient, constituent or scheduled substance listed on the Public Chemical Registration Information System Search (PubCRIS).[12]

[8] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[9] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[10] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[11] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[12] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris

International regulations

- Products containing a fixed-dose combination of azelastine and fluticasone propionate are registered in 40 countries worldwide[13,14].
- In Canada[15], the United States of America[16], the United Kingdom[17] and many countries in the European Union (EU)[18] , products containing this combination of active ingredients are controlled as prescription only medicines.
- According to the New Zealand Medicines and Medical Devices Safety Authority (MedSafe) azelastine and fluticasone are available as follows in New Zealand[19]:

Ingredient	Conditions	Classification
azelastine	**except** when specified elsewhere in this schedule	Prescription
azelastine	in preparations for nasal use containing 0.15% azelastine hydrochloride or less; and in topical eye preparations containing 0.05% or less	Pharmacy Only
fluticasone	**except** when specified elsewhere in this schedule	Prescription
fluticasone	for the treatment or prophylaxis of allergic rhinitis in adults and children over 12 years of age when in aqueous nasal sprays delivering up to 50 micrograms per actuation with a maximum recommended daily dose of 200 micrograms (as a single dose)	Pharmacy Only

[13] European Medicines Agency (EMA) https://www.ema.europa.eu/en/documents/psusa/azelastine/fluticasone-list-nationally-authorised-medicinal-products-psusa/00010067/201510_en.pdf
[14] Martindale [online via MedicinesComplete]: https://about.medicinescomplete.com/publication/martindale-the-complete-drug-reference/
[15] Canadian (Health Canada) Drug Product Database https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[16] FDA Approved Drug Products Database https://www.accessdata.fda.gov/scripts/cder/daf/
[17] Medicines and Healthcare products Regulatory Agency (MHRA) electronic medicines compendium (emc) https://www.medicines.org.uk/emc/product/9450/smpc#gref
[18] European Medicines Agency (EMA), https://www.ema.europa.eu/en/documents/psusa/azelastine/fluticasone-list-nationally-authorised-medicinal-products-psusa/00010067/201510_en.pdf
[19] New Zealand Medicines and Medical Devices Safety Authority (MedSafe) https://www.medsafe.govt.nz/profs/class/classintro.asp

3 Proposed amendments referred for scheduling advice to the Joint ACMS-ACCS #30

3.1 Cannabis and tetrahydrocannabinols

Proposal

The applicant has proposed the introduction of Schedule 7 entries for cannabis and tetrahydrocannabinols for use in analytical and scientific research. The amended entries would allow access to cannabis and its derivatives for use in research without Schedule 9 requirements, which can include specific approval from State and Territory health departments.

CAS Number:

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

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

5957-75-5 (Delta-8-tetrahydrocannabinol)

13956-29-1 (Cannabidiol)

521-35-7 (Cannabinol)

Alternative names

Marijuana

Applicant

Private applicant

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

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.

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CANNABIS
cross reference: CANNABIS SATIVA, HEMP, HEMP SEED OIL, TETRAHYDROCANNABINOLS

Schedule 9
Schedule 8
Appendix D, Item 1
Appendix K

TETRAHYDROCANNABINOLS
cross reference: CANNABIS, HEMP SEED OIL, NABIXIMOLS

Schedule 9
Schedule 8
Appendix D, Item 1
Appendix K

Proposed scheduling

The applicant is seeking to introduce new entries in Schedule 7 and Appendix J for cannabis and tetrahydrocannabinols as follows:

Cannabis

Schedule 7 – New Entry

CANNABIS (including seeds, extracts, resins and the plant, and any part of the plant) for analytical and scientific research, and excluding human or veterinary therapeutic use, when present in:

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

b) imported for the purpose of analytical and scientific research; and/or

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

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

except when

i) separately specified in the NABIXIMOLS in Schedule 8; or

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

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

iv) hemp seed oil containing 75 mg/kg or less of cannabidiol and 10 mg/kg or less of tetrahydrocannabinols.

Appendix J – New Entry

Poisons	Authorisation considerations
CANNABIS	a

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CANNABIS
cross reference: CANNABIS SATIVA, HEMP, HEMP SEED OIL, TETRAHYDROCANNABINOLS

Schedule 9
Schedule 8
Schedule 7
Appendix D, Item 1
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Appendix K

Tetrahydrocannabinol

Schedule 7 – New Entry

TETRAHYDROCANNABINOLS, including carboxylic acid forms and the decarboxylated forms, when extracted or manufactured from cannabis and for use for analytical and scientific research, and excluding any human or veterinary therapeutic use, when present in:

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

b) material imported for the purpose of analytical and scientific research; and/or

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

d) 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) hemp seed oil at a concentration of 10 mg/kg or less.

Appendix J – New Entry

Poisons	Authorisation considerations
TETRAHYDROCANNABINOL	a

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TETRAHYDROCANNABINOLS
cross reference: CANNABIS, HEMP SEED OIL, NABIXIMOLS

Schedule 9
Schedule 8
Schedule 7
Appendix D, Item 1
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Key uses / expected use

Medicines

Background

Cannabis is a term used to describe a range of varieties of the Cannabis genus. The Cannabis plant produces a resin containing compounds called cannabinoids. Some cannabinoids possess psychoactive properties.

Cannabis contains about 60 cannabinoids, of which the main active constituent is delta-9-tetrahydrocannabinol. Delta-9-tetrahydrocannabinol (THC) reportedly has anti-emetic properties and has been associated with claims relating to use for the control of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional anti-emetics. Another active cannabinoid present in Cannabis is cannabidiol that is associated with claims relating to use as an analgesic, anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, anti-oxidant and anti-psychotic. Delta-8-tetrahydrocannabinol (delta-8-THC) is a component of C*annabis sativa* which is produced naturally in very small quantities as a degradation product of THC but can be synthesised from cannabidiol[20]. The lack of regulatory oversight in the production and supply of delta-8-THC is

[20] Arno Hazekamp et. Al 2010, *Chemistry of Cannabis*, Comprehensive Natural Products II, Elsevier, 2010,

currently of concern to the United States Food and Drug Administration (FDA), who have reported an increase in adverse effect reporting regarding this substance[21].

Application summary – reasons for proposal

Cannabis and tetrahydrocannabinols fall under Schedule 9 of the Poisons Standard when used for research and analytics. The manufacture, possession, sale or use of these substances is prohibited by law except when required for medical or scientific research, or for analytical, teaching or training purposes with approval of Commonwealth and/or State or Territory Health Authorities.

The reasons from the applicant are as follows:

- Schedule 7 entries for cannabis and tetrahydrocannabinols will facilitate foundational and preclinical research of these substances without Schedule 9 controls.
- These substances are available in the Poisons Standard for therapeutic use in humans, and the proposed changes specify use only for research and analytics necessary to support and further therapeutic use.
- The proposal does not intend inclusion of any synthetic isomer of tetrahydrocannabinol which does not normally occur within the cannabis plant.
- Human or animal therapeutic use would be excluded under the proposed Schedule 7 listing. The application also proposed that cannabis and tetrahydrocannabinol are added to Appendix J - Schedule 7 Poisons Requiring Additional Controls on Availability of Use, Part 2 with an authorisation consideration of 'a' (restricted to analytical or research purposes only).
- Specialist analytical laboratories are experienced in, and have the skills, infrastructure and licences to handle Schedule 7 Dangerous Poisons. The risk of diversion of samples and standards required to undertake analytics and research (including preclinical animal studies) would appear to be small.
- The provisions in Parts 1 – 3 of the Poisons Standard pertaining to a Schedule 7 Dangerous Poison, appear appropriate for cannabis and tetrahydrocannabinol for analytical and research purposes, with regards to labelling, containers, storage, disposal, record keeping, restrictions on sale, supply, possession and use, and advertising.

Australian regulations

- According to the TGA Ingredient Database,[22] 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.

[21] U.S. Food and Drug Administration, https://www.fda.gov/consumers/consumer-updates/5-things-know-about-delta-8-tetrahydrocannabinol-delta-8-thc
[22] TGA Ingredient Database https://www.ebs.tga.gov.au/

- According to the TGA Ingredient Database,[23] cannabidiol is:
  - Available for use as an active ingredient in export only, over-the-counter and prescription medicines;
  - Not available as an excipient ingredient in any application;
  - Not available as an equivalent ingredient in any application.
- According to the TGA Ingredient Database,[24] delta-9-tetrahydrocannabinol is:
  - Available for use as an active ingredient in export only and prescription medicines;
  - Not available as an excipient ingredient in any application;
  - Available as an equivalent ingredient in export only and prescription medicines.
- Delta-8-tetrahydrocannabinol is not captured in the TGA Ingredient Database[25].
- As of December 2021, there were 78 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[26] that contain *Cannabis sativa*, cannabidiol and/or tetrahydrocannabinol as active ingredients.
- As of December 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[27] No. 3 of 2021.
- Cannabis and tetrahydrocannabinols are not included in the TGA prescribing medicines in pregnancy database[28].
- There are no warning statements pertaining to cannabis or tetrahydrocannabinols in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[29].
- As of December 2021, there were 108 reports of adverse events for products containing cannabis and/or cannabinoids as an active ingredient on the Database of Adverse Event Notifications (DAEN),[30] with 93 reports where cannabis or cannabinoids were the single suspected ingredient. The adverse events reported are varied in nature, affecting multiple organ systems.
- As of December 2021, there were no products containing cannabis and/or tetrahydrocannabinols listed on the Public Chemical Registration Information System Search (PubCRIS)[31].
- Unapproved medicinal cannabis products imported into and supplied/manufactured in Australia must conform with the Therapeutic Goods (Standard for Medicinal Cannabis) (TGO93) Order 2017. TGO 93 is a standard that specifies minimum quality requirements for medicinal cannabis products.

[23] TGA Ingredient Database https://www.ebs.tga.gov.au/
[24] TGA Ingredient Database https://www.ebs.tga.gov.au/
[25] TGA Ingredient Database https://www.ebs.tga.gov.au/
[26] ARTG database https://www.tga.gov.au/artg
[27] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[28] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[29] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[30] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[31] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris

International regulations

- United States Food and Drug Administration Approved Drug Products Database (Drugs@FDA)[32] regulate cannabidiol as a prescription only medicine.
- Cannabis and tetrahydrocannabinols are not included in the WHO Model List of Essential Medicines 2019.[33]
- Cannabidiol and delta-9-tetrahydrocannabinol are approved for use as prescription-only human medicines in Canada, according to the Canadian (Health Canada) Drug Product Database.[34]
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe),[35] Cannabis sativa is a Class C1 Controlled Drug in New Zealand. Tetrahydrocannabinol and delta-9-tetrahydrocannabinol are Class B1 Controlled Drugs.

3.2 Lead

Proposal

The applicant has proposed that the entries for lead and lead compounds in Schedules 4, 5 and 6 be removed, and preparations including medicines and cosmetics that contain lead be captured in an expanded Schedule 10 entry. Further amendments aimed at reducing or eliminating lead in consumer products are proposed for Appendix A for printing inks or ink additives, Appendix B for metallic lead, and the entries for lead compounds in Appendices E and F. These changes will prohibit the presence of lead in any of the specified products.

CAS Number:

7439-92-1 (elemental)

Alternative names

N/A

Applicant

Private applicant

[32] FDA Approved Drug Products Database https://www.accessdata.fda.gov/scripts/cder/daf/
[33] WHO Model List of Essential Medicines 2019: https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06
[34] Canadian (Health Canada) Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[35] New Zealand Medicines and Medical Devices Safety Authority (Medsafe): https://www.medsafe.govt.nz/profs/class/classintro.asp

Current scheduling

Lead is currently in Schedules 4, 5, 6 and 10 of the Poisons Standard as follows:

Schedule 10

LEAD COMPOUNDS:

a) in anti-fouling or anti-corrosive paints **except** in preparations containing 0.1 per cent or less of lead calculated on the non-volatile content of the paint; or

b) in paints (other than anti-fouling or anti-corrosive paints), tinters, inks or ink additives **except** in preparations containing 0.009 per cent or less of lead calculated on the non-volatile content of the paint, tinter, ink or ink additive.

Schedule 6

LEAD COMPOUNDS **except**:

a) when included in Schedule 4 or 5;

b) in paints, tinters, inks or ink additives;

c) in preparations for cosmetic use containing 100 mg/kg or less of lead;

d) in pencil cores, finger colours, showcard colours, pastels, crayons, poster paints/colours or coloured chalks containing 100 mg/kg or less of lead; or

e) in ceramic glazes when labelled with the warning statement:

CAUTION – Harmful if swallowed. DO not use on surfaces which contact food or drink.

Written in letters not less than 1.5 mm in height.

Schedule 5

LEAD COMPOUNDS in preparations for use in hair cosmetics.

Schedule 4

LEAD for human therapeutic use.

Lead is also included in the Appendices as follows:

Appendix A

PRINTING INKS or INK ADDITIVES except:

a) when containing a pesticide; or

b) preparations containing more than 0.1 per cent of lead calculated on the non-volatile content of the ink or ink additive.

Appendix B, Part 3

LEAD METALLIC ("Low Toxicity" for any use)

Appendix E, Part 2

LEAD COMPOUNDS

- in hair cosmetics: Standard statement 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).)
- in other preparations: Standard statements A and S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.)

Appendix F, Part 3

LEAD COMPOUNDS

a) in hair cosmetics: Warning statement 25 (Do not use on broken skin. Wash hands thoroughly after use.)

b) when in Schedule 6: Safety directions 1 (Avoid contact with eyes), 4 (Avoid contact with skin) and 8 (Avoid breathing dust (or) vapour (or) spray mist.)

Proposed scheduling

Schedule 10 – Amend Entry

LEAD COMPOUNDS:

a) in anti-fouling or anti-corrosive ~~paints~~ primers **except** in preparations containing 0.1 per cent or less of lead calculated on the non-volatile content of the ~~paint~~ primer; or

b) in paints (other than anti-fouling or anti-corrosive ~~paints~~ primers), tinters, inks or ink additives **except** in preparations containing 0.009 per cent or less of lead calculated on the non-volatile content of the paint, tinter, ink or ink additive; or

c) in preparations for cosmetic use; or

d) for therapeutic use; or

e) in roofing where rainwater is collected into a potable water tank.

A similar amendment concerning paints should be made to Part 2, Section Seven, sub paragraphs (2)(a) and (b).

Schedule 6 – Amend Entry

LEAD COMPOUNDS (including LEAD METALLIC) **except**:

a) when included in Schedule 4 or 5;

b) in paints, tinters, inks or ink additives;

c) in preparations for cosmetic use containing 100 mg/kg or less of lead;

d) in pencil cores, finger colours, showcard colours, pastels, crayons, poster paints/colours or coloured chalks containing 100 mg/kg or less of lead; or

e) in ceramic glazes when labelled with the warning statement:

CAUTION – Harmful if swallowed. DO not use on surfaces which contact food or drink.

Written in letters not less than 1.5 mm in height.

f) In leaded brass containing not less than 0.25 per cent of lead when labelled with the warning statement:

CAUTION – This plumbing product contains leaded brass and may add lead to water which would then be harmful if imbibed. Do not use in areas with potable water of greater than average acidity, alkalinity or softness.

g) In leaded brass containing less than 0.25 per cent of lead when labelled with the warning statement:

CAUTION – This plumbing product contains low-leaded brass and may add lead to water which would then be harmful if imbibed. Do not use in areas with potable water of greater than average acidity, alkalinity or softness.

Schedule 5 – Delete Entry

~~LEAD COMPOUNDS in preparations for use in hair cosmetics.~~

Schedule 4 – Delete Entry

~~LEAD for human therapeutic use.~~

Appendix A – Amend Entry

PRINTING INKS or INK ADDITIVES except:

a) when containing a pesticide; or

b) preparations containing more than ~~0.1~~0.009 per cent of lead calculated on the non-volatile content of the ink or ink additive.

Appendix B, Part 3 – Amend Entry

LEAD METALLIC **except** when separately specified elsewhere in the Schedules.

Appendix E, Part 2 – Amend Entry

LEAD COMPOUNDS

- ~~in hair cosmetics: Standard statement 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).)~~
- in other preparations: Standard statements A and S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.)

Appendix F, Part 3 – Amend Entry

LEAD COMPOUNDS

a) in hair cosmetics: Warning statement 25 (Do not use on broken skin. Wash hands thoroughly after use.)

b) when in Schedule 6: Safety directions 1 (Avoid contact with eyes), 4 (Avoid contact with skin) and 8 (Avoid breathing dust (or) vapour (or) spray mist.)

Key uses / expected use

Domestic and industrial, animal and homeopathic uses

Background

This proposal follows on from the application considered at the March 2021 meeting of the Advisory Committee on Chemicals Scheduling (ACCS), received from the same applicant. While the March application focused on the levels of lead permissible in paint, this new application expands the scope to address other instances of lead in the Poisons Standard by prohibiting the presence of lead in a range of consumer products including cosmetics and therapeutic goods.

Application summary - reasons for proposal

The reasons from the applicant are as follows:

- Lead is highly toxic in all chemical forms and should be eliminated from hair cosmetics altogether as child lead exposure has been demonstrated to occur when adults use leaded hair cosmetics in a home shared with children.
- Lead is the most studied toxic substance and the subject of both United Nations and World Health Organization partnerships to create a lead-safe world. Due to the findings of decades of research into lead's toxicity, Lead can no longer be regarded to have any therapeutic use and the designation of "Low toxicity" in relation to the addition of metallic lead for any general use is outdated.
- Lead is now known to be toxic at much lower concentrations than previously thought and can no longer be considered to have any therapeutic uses. In cosmetic uses, paints and inks, lead can easily become accessible to workers, DIY-renovators, other adults and children so should be banned or limited in all cases, including hair cosmetics and coatings applied on top of anti-corrosive primers.
- Even low levels of exposure to lead have demonstrated harmful effects. Known health effects include anaemia, hypertension, kidney damage, reduced IQ and behavioural changes. Exposure in adults is associated with increased risk of cardiovascular disease, including hypertension and coronary heart disease.
- The Institute for Health Metrics and Evaluation estimated that, in 2017, lead exposure accounted for 1.06 million deaths and the loss of 24.4 million years of healthy life (disability-adjusted life years) worldwide. Lead is a well-documented ecotoxicant, posing threats to both aquatic and terrestrial ecosystems.

Australian regulations

- According to the TGA Ingredient Database,[36] lead is:
  - Available for use as an active ingredient in biologicals, export only, listed medicines, over the counter and prescription medicines.
    - In listed medicines, this use is permitted to be homeopathic only.
  - Available for use as an excipient ingredient in biologicals, devices and prescription medicines.
  - Available for use as an equivalent ingredient in listed medicines.
- As of December 2021, there were no medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[37] that contain lead as an active ingredient.
- According to the Therapeutic Goods (Permissible Ingredients) Determination[38] No.3 of 2021, lead is permitted to be included in listed medicines as follows:

Item	Ingredient name	Purpose	Specific requirements
2980	LEAD	H	Only for use as an active homoeopathic ingredient. The concentration in the medicine must be no more than 0.001%.
2981	LEAD ACETATE	H	Only for use as an active homoeopathic ingredient.
4168 4169 4170 4171 4172 4173	PROPOLIS PROPOLIS BALSAM PROPOLIS DRY EXTRACT PROPOLIS LIQUID EXTRACT PROPOLIS RESIN PROPOLIS TINCTURE	A, E A, E A, E A, E A, E A, E	Lead is a mandatory component of (these ingredients). The concentration of lead in the medicine must be no more than 0.001%. When used topically, the medicine requires the following warning statement on the medicine label: (PROP1) 'WARNING: Propolis may cause skin irritation. Test before use' When used for other than for topical, the medicine requires the following warning statement on the medicine label: (PROP2) 'Warning: Propolis may cause allergic reactions. If irritation or swelling of the mouth or throat occurs, discontinue use.'
A = active ingredient for a medicine has the same meaning as in the Regulations H = homoeopathic preparation ingredient meaning an ingredient that is a constituent of a homoeopathic preparation			

[36] TGA Ingredient Database https://www.ebs.tga.gov.au/
[37] ARTG database https://www.tga.gov.au/artg
[38] Therapeutic Goods (Permissible Ingredients) Determination
https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination

- The TGA prescribing medicines in pregnancy database[39] does not have an entry for lead.
- There are no warning statements pertaining to lead in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[40].
- As of December 2021, there were no reports of adverse events for products containing lead as an active ingredient on the Database of Adverse Event Notifications (DAEN)[41].
- As of December 2021, there were two entries containing lead listed on the Public Chemical Registration Information System Search (PubCRIS)[42] (as lead acetate). Lead acetate is listed as an approved active constituent and listed as an active constituent in a dermatological veterinary medicine.
- In 2009-2019 no adverse experiences were recorded for lead in the APVMA Adverse Experience Reporting Program database (AERP).[43]

International regulations

- Lead is not listed on the Food and Drugs Administration Approved Drugs Database[44] or the Health Canada Drug Product Database[45].
- According to the Medsafe Medicine Classification Database[46], lead is regulated as a prescription medicine.
- The European Chemicals Agency[47] (ECHA) lists lead as a 'substance of very high concern'. Hazard classifications include "may damage fertility or the unborn child, causes damage to organs through prolonged or repeated exposure, is very toxic to aquatic life with long lasting effects, may cause cancer, is very toxic to aquatic life and may cause harm to breast-fed children".
- The European Commission's Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP)[48] is of the opinion that lead acetate should not be intentionally added to cosmetic products.

3.3 Meloxicam

Proposal

The applicant has proposed that a new Schedule 6 entry be created for meloxicam that captures oral transmucosal preparations, at up to 1 per cent concentration, for pre-surgical treatment and pain management during routine animal husbandry procedures. The new entry would allow access to meloxicam without a prescription for pain relief in animals undergoing these procedures.

[39] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[40] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[41] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[42] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[43] APVMA Adverse Experience Reporting Program database (AERP) https://apvma.gov.au/node/10946
[44] Food and Drugs Administration Approved Drugs Database https://www.accessdata.fda.gov/scripts/cder/daf/
[45] Health Canada Drug Product Database https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[46] Medsafe Medicines Classification Database https://www.medsafe.govt.nz/profs/class/classintro.asp
[47] European Chemicals Agency https://echa.europa.eu/substance-information/-/substanceinfo/100.028.273
[48] SCCNFP on lead acetate https://ec.europa.eu/health/ph_risk/committees/sccp/documents/out286_en.pdf

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 oral transmucosal preparations containing 1 per cent or less meloxicam for pre-surgical treatment and pain management during routine animal husbandry procedures.

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

Background

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class. It is a selective cycloxygenase-2-(COX-2) inhibitor, which acts by inhibiting the synthesis of prostaglandins that induce inflammation, pain, and fever, and, thereby, exerts anti-inflammatory, anti-endotoxic, anti-exudative, analgesic and antipyretic effects.

The application proposes an amendment to Schedule 4, and a new entry in Schedule 6 for meloxicam for preparations containing meloxicam in an oral transmucosal formulation, for use to alleviate pain associated with routine husbandry procedures. This application follows one that was discussed at the Joint ACMS-ACCS meeting in November 2021 which proposed an entry in Schedule 6 for low concentration injectable preparations of meloxicam for pain relief for sheep undergoing husbandry procedures.

Application summary - reasons for proposal

The reasons from the applicant are as follows:

- The product is administered orally as a single dose and farmers are generally experienced at administering medications to their livestock by oral dosing. The risks from misuse, abuse or illicit use, adverse effects and interactions are managed by the appropriate labelling including safety directions, first aid and additional user safety statements, and packaging for single use prior to routine husbandry procedures.
- The acute toxicity profile of meloxicam is consistent with a Schedule 6 classification, based on various acute oral toxicity studies in rats, rabbits, mice and minipigs. Short term repeat dose studies demonstrated gastrointestinal (GI) ulceration and haemorrhage and renal degeneration. GI lesions were observed in long-term studies, with ulcerous colitis or peritonitis in the small intestine and gastritis in the stomach of test subjects.
- The potential for diversion of veterinary preparations of meloxicam to use in humans is low, considering the high availability and relatively low cost of meloxicam for human therapeutic use.
- The application is based on a liquid oral meloxicam product that was first registered in Australia in 2015. The APVMA Adverse Experience Reporting Program has not received any adverse experience reports involving the product since its initial registration.

Australian regulations

- According to the TGA Ingredient Database,[49] 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 December 2021, there were 71 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[50] 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[51] No.3 of 2021.

[49] TGA Ingredient Database https://www.ebs.tga.gov.au/
[50] ARTG database https://www.tga.gov.au/artg
[51] Therapeutic Goods (Permissible Ingredients) Determination: https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination

- The TGA prescribing medicines in pregnancy database[52] 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[53].
- In November 2011 – November 2021, there were 250 reports of adverse events for products containing meloxicam as an active ingredient on the Database of Adverse Event Notifications (DAEN),[54] with 144 reports where meloxicam was the single suspected medicine. Gastrointestinal disorders accounted for 138 reports (55%); these included gastrointestinal haemorrhage, melaena, nausea, haematemesis and vomiting.
- As of December 2021, there were 56 products containing meloxicam listed on the Public Chemical Registration Information System Search (PubCRIS)[55], 25 of which are oral suspensions, pastes, or gels for buccal administration.
- In 2015 – 2020, the following adverse experiences were recorded for meloxicam in the APVMA Adverse Experience Reporting Program database (AERP)[56].
  - 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.[57]
- The Health Products Regulatory Authority of Ireland[58] regulates meloxicam as a prescription-only medicine.
- The United States Food and Drug Administration[59] 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.[60]

[52] TGA prescribing medicines in pregnancy database: https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[53] Therapeutic Goods (Medicines Advisory Statements) Specification 2019: https://www.legislation.gov.au/Details/F2019L00213
[54] Database of Adverse Event Notifications (DAEN): https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[55] Public Chemical Registration Information System Search (PubCRIS): https://portal.apvma.gov.au/pubcris
[56] APVMA Adverse Experience Reporting Program database (AERP) https://apvma.gov.au/node/10946
[57] WHO Model List of Essential Medicines 2019: https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06
[58] Health Products Regulatory Authority of Ireland: https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/
[59] United States Food and Drug Administration: https://www.accessdata.fda.gov/scripts/cder/daf/
[60] 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),[61] meloxicam is available as a prescription-only medicine in New Zealand.

3.4 Lidocaine

Proposal

The applicant has proposed that the existing Schedule 5 entry for lidocaine be amended to exclude injectable formulations for veterinary use in certain husbandry procedures. The proposal effectively seeks to reverse the scheduling decision on lidocaine published in September 2021.

CAS Number:

137-58-6

Alternative names

2-(Diethylamino)-*N*-(2,6-dimethylphenyl)acetamide, 2-diethylamino-2′,6′-acetoxylidide; ω-diethylamino-2,6-dimethylacetanilide; lignocaine

Applicant

Private applicant

Current scheduling

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

Schedule 4

LIDOCAINE **except**:

a) when included in Schedules 2 or 5;

b) in dermal preparations containing 2 per cent or less of total local anaesthetic substances per dosage unit; or

c) in lozenges containing 30 mg or less of total anaesthetic substances per dosage unit.

Schedule 2

LIDOCAINE in preparations for topical use other than eye drops:

a) containing 10 per cent or less of total local anaesthetic substances, except:

i) in dermal preparations containing 2 per cent or less of total local anaesthetic substances; or

ii) in aqueous sprays for oromucosal use containing 0.6 per cent or less of total local anaesthetic substances; or

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

b) in divided preparations containing 200 mg or less of total local anaesthetic substances, except in lozenges containing 30 mg or less of total local anaesthetic substances per dosage unit.

Schedule 5

LIDOCAINE:

a) in aqueous gel preparations containing 4.5 per cent or less of lidocaine, for the dermal spray-on administration to the wounds of animals; or

b) in injectable preparations containing 2 per cent or less of lidocaine when packaged in a container with a tamper resistant cartridge which can only be dispensed through a rubber ring applicator for tail docking and castration of lambs; or castration of calves.

Proposed scheduling

Schedule 4

LIDOCAINE **except**:

a) when included in Schedules 2 or 5;

b) in dermal preparations containing 2 per cent or less of total local anaesthetic substances per dosage unit; or

c) in lozenges containing 30 mg or less of total anaesthetic substances per dosage unit.

Schedule 2

LIDOCAINE in preparations for topical use other than eye drops:

a) containing 10 per cent or less of total local anaesthetic substances, except:

   i) in dermal preparations containing 2 per cent or less of total local anaesthetic substances; or

   ii) in aqueous sprays for oromucosal use containing 0.6 per cent or less of total local anaesthetic substances; or

b) in divided preparations containing 200 mg or less of total local anaesthetic substances, except in lozenges containing 30 mg or less of total local anaesthetic substances per dosage unit.

Schedule 5 – Amend Entry

LIDOCAINE

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

b) in injectable preparations containing 2 percent or less of lidocaine when packaged in a bottle with a tamper proof cartridge for use in conjunction with a rubber ring applicator for tail docking and castration of lambs; or castration of calves.

Key uses / expected use

Veterinary (local anaesthetic)

Background

Lidocaine, also known as lignocaine, is a local anaesthetic of the amino amide type. It has a rapid onset of action and is commonly used as a nerve block during routine surgeries, particularly for dental or topical operations, or for relief from localised pain. This application seeks to remove the Schedule 5 entry for injectable preparations of lidocaine for use in sheep husbandry procedures, which was introduced into the Poisons Standard in October 2021.

Application summary - reasons for proposal

The reasons from the applicant are as follows:

- The application expresses concern regarding the "tamper-resistant" condition placed on packaging of Schedule 5 preparations of lidocaine, as this can be circumvented by dispensing of the solution into a vessel to be used for purposes other than those specified in the Schedule 5 entry. The applicant claims that these risks are manageable under a Schedule 4 listing.
- Misuse of lidocaine poses public health risks, including as an unregulated anaesthetic by illegal "body modifiers", in the dilution ("cutting") of cocaine by illicit drug manufacturers, and as a suicide agent[62].
- There is also concern regarding animal welfare, with the prospect of lidocaine being used as a masking agent in performance animals or to perform painful acts of veterinary science, with poor animal welfare outcomes.
- Access to lidocaine for use by farmers on livestock is not impeded by the involvement of veterinarians, and veterinary oversight of the quantities and use of the substance is important to mitigate the risks of misuse or diversion.

Australian regulations

- According to the TGA Ingredient Database[63], lidocaine is:
  - Available for use as an active ingredient in biologicals, export only, over the counter and prescription medicines, as anhydrous, hydrochloride and hydrochloride monohydrate;
  - Available for use as an excipient in biologicals, devices and prescription medicines, as anyhydrous, hydrochloride and hydrochloride monohydrate;
  - Available as an equivalent ingredient as anhydrous or hydrochloride.
- As of December 2021, there were 193 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[64] that contain lidocaine as an active ingredient. These include 53 prescription and 84 non-prescription medicines, 35 devices, and 21 products for export only. Formulations include injections in 0.5%, 1% and 2% strengths (with and without

[62] Suicide due to oral ingestion of lidocaine: a case report and review of the literature pubmed.ncbi.nlm.nih.gov/16787726/
[63] TGA Ingredient Database https://www.ebs.tga.gov.au/
[64] ARTG database https://www.tga.gov.au/artg

adrenaline), gels in 2%, 2.5% and 5% strengths, ointments in 5% and 10% strengths, creams in 4% and 5% strengths, lotions, oral liquids, jellies, paints, sprays/aerosols, pellets, dermal patches, eye drops and lozenges.

- Lidocaine is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[65] No.3 of 2021.
- The TGA prescribing medicines in pregnancy database[66] classifies lidocaine as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Lidocaine	A	Cardiovascular System	Antiarrhythmics	
Lidocaine	A	Drugs Used in Anaesthesia	Local anaesthetics	
Lignocaine (lidocaine)	A	Cardiovascular System	Antiarrhythmics	
Lignocaine (lidocaine)	A	Drugs Used in Anaesthesia	Local anaesthetics	
Category A – Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.				

- The Therapeutic Goods (Medicines Advisory Statements) Specification 2019[67] requires the following warning statements pertaining to lidocaine to be included on the labelling:

Substance	Conditions	Required Statement(s)
Lidocaine (lignocaine) (*Entry 1 of 3*)	In dermal preparations containing MORE THAN 2 per cent of total local anaesthetic substances	Do not apply to large areas of the body, except on the advice of a healthcare practitioner. If skin irritation occurs, discontinue use and seek advice from your doctor or pharmacist.
Lidocaine (lignocaine) (*Entry 2 of 3*)	In dermal preparations containing 2 per cent OR LESS of total local anaesthetic substances	If skin irritation occurs, discontinue use and seek advice from your doctor or pharmacist.

[65] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[66] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[67] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213

Lidocaine (lignocaine) (*Entry 3 of 3*)	In lozenges	Do not take hot food or drink if the mouth feels numb after taking this product as it may burn the mouth. Do not give to children under 6 years of age, unless recommended by a doctor, pharmacist or dentist.

- Since November 2011, there have been 248 reports of adverse events for products containing lidocaine as an active ingredient on the Database of Adverse Event Notifications (DAEN),[68] with 131 reports where lidocaine was the single suspected medicine. 78 reports (31%) were due to skin and subcutaneous tissue disorders such as rash, urticaria, pruritus and angioedema.
- As of December 2021, there were 15 products containing lidocaine (as lignocaine) listed on the Public Chemical Registration Information System Search (PubCRIS)[69] in a variety of formulations, including injections, topical solutions, creams, ear drops and sprays.
- In 2015 – 2020, the following adverse experiences were recorded for lignocaine in the APVMA Adverse Experience Reporting Program database (AERP):[70]
  - Four reports of serious incidents classified as related to animal health;
  - Two reports of serious incidents classified as related to human health; and
  - One report of a serious incident classified as related to efficacy.

International regulations

- According to the United States Food and Drug Administration Approved Drug Products Database[71], lidocaine is approved for use as a prescription medicine in the United States.
- Lidocaine is approved as an over the counter and prescription medicine in Canada according to the Canadian (Health Canada) Drug Product Database[72].
- The Health Products Regulatory Authority of Ireland[73] lists lidocaine as a prescription only medicine in most formulations, although some preparations (e.g. creams of less than 5% lidocaine) are available over the counter.

[68] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[69] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[70] APVMA Adverse Experience Reporting Program database (AERP) https://apvma.gov.au/node/10946
[71] Food and Drug Administration Approved Drugs Database: https://www.accessdata.fda.gov/scripts/cder/daf/
[72] Health Canada Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[73] Health Products Regulatory Authority https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?page=1&field=ACTIVESUBSTANCES&query=Lidocaine

- According to the New Zealand Medicines and Medical Devices Safety Authority (MedSafe)[74], lidocaine (as lignocaine) is regulated as follows:

Ingredient	Conditions	Classification
Lignocaine	• for injection **except** when used as a local anaesthetic in practice by a nurse whose scope of practice permits the performance of general nursing functions or by a podiatrist registered with the Podiatry Board or by a dental therapist or oral health therapist registered with the Dental Council; • for ophthalmic use **except** when used in practice by an optometrist registered with the Optometrists and Dispensing Opticians Board; for oral use **except** in throat lozenges in medicines containing 30 milligrams or less per dose form; for external use in medicines containing more than 10%; • **except** in throat sprays in medicines containing 2% or less; • **except** when specified elsewhere in this schedule	Prescription
Lignocaine	• for urethral use; • for external use in medicines containing 10% or less and more than 2%	Pharmacy Only
Lignocaine	• in throat lozenges in medicines containing 30 milligrams or less per dose form; • for external use in medicines containing 2% or less; • in throat sprays in medicines containing 2% or less	General Sale

[74] Medsafe Medicine Classification Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp

4 Proposed amendments referred for scheduling advice to ACCS #33

The TGA has received two applications to amend the Poisons Standard with respect to flumioxazin.

4.1 Flumioxazin (private application)

Proposal

The applicant proposed that the Schedule 6 entry for flumioxazin be amended to include liquid preparations. Liquid preparations of flumioxazin are currently captured in the Schedule 7 entry. The amended entry would allow access to liquid preparations of flumioxazin to be available without the requirement for a prescription.

CAS Number:

103361-09-7

Alternative names

2-[7-Fluoro-3,4-dihydro-3-oxo-4-(2-propyn-1-yl)-2*H*-1,4-benzoxazin-6-yl]-4,5,6,7-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione; *N*-(7-fluoro-3,4-dihydro-3-oxo-4-prop-2-ynyl-2*H*-1,4-benzoxazin-6-yl)cyclohex-1-ene-1,2-dicarboximide

Applicant

Private applicant

Current scheduling

Flumioxazin is currently listed in Schedules 6 and 7 of the Poisons Standard as follows:

Schedule 7

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

Schedule 6

FLUMIOXAZIN when contained in water soluble bags individually packed in sealed sachets.

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FLUMIOXAZIN

Schedule 7
Schedule 6

Proposed scheduling

Schedule 6 – Amend Entry

FLUMIOXAZIN in liquid formulations or when contained in water soluble bags individually packed in sealed sachets.

Background

Flumioxazin is a member of the N-phenyl-imides group of herbicides. It acts by reducing the enzyme activity of protoporphyrinogen oxidase, which is critical in the chlorophyll synthetic pathway, causing affected plants to decompose. The proposal seeks to increase access to preparations of this substance, which is currently subject to Schedule 7 restrictions (as specified in state and territory legislation), except when presented in water soluble bags.

Application summary - reasons for proposal

The reasons from the applicant are as follows:

- There is extensive information available outlining the toxicological profile of flumioxazin. Flumioxazin has low oral, dermal and inhalational toxicity, is not a skin irritant, is a slight eye irritant, and is not a skin sensitiser.
- Flumioxazin is currently included in Schedule 7 in all formulations except when presented in water soluble bags, due to the associated irreversible developmental and reproductive effects, chronic hepatotoxicity, and the induction of porphyria and potential for photodermatitis.
- In 2011, flumioxazin supplied in water soluble packaging was added to Schedule 6 of the Poisons Standard. The Delegate concluded that risk mitigation had been adequately established for preparations in water soluble bags when individually packed in sealed sachets through estimated worker exposure, which resulted in an adequate margin of exposure (MOE) due to the significantly reduced risk of contact with the product in such packaging.
- Liquid formulations of flumioxazin packaged as a suspension concentrate (SC) should also be in Schedule 6 based in the toxicological profile of the product and the modelled worker exposure which demonstrates adequate MOEs.
- Previous scheduling decisions with respect to saflufenacil and carbetamide, that have similar toxicology profiles and use patterns to flumioxazin SC, indicate that a Schedule 6 entry is appropriate.
- Flumioxazin in a liquid formulation will have the same exposure and risk as water soluble packaging, except for mixing and loading. However, with label warnings and use of Personal Protective Equipment (PPE), the risk can be mitigated.
- The liquid formulation has practical advantages for growers compared to a granular formulation (in water soluble bags) as the product is easy to measure and add to the spray tank during mixing and application. The product is intended for professional use only and not available to the general public.

Key uses / expected use

Agriculture

Australian regulations

- Flumioxazin is not included in the TGA Ingredient Database[75].
- As of 30 November 2021, there were zero medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[76] that contain flumioxazin as an active ingredient.
- Flumioxazin is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[77] No.3 of 2021.
- Flumioxazin is not included in the TGA prescribing medicines in pregnancy database.[78]
- There are no warning statements pertaining to flumioxazin in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[79].
- As of December 2021, there were no reports of adverse events for products containing flumioxazin as an active ingredient on the Database of Adverse Event Notifications (DAEN).[80]
- As of December 2021, there were 22 products containing flumioxazin listed on the Public Chemical Registration Information System Search (PubCRIS).[81]
- In 2015-2020 there were no adverse experiences were recorded for flumioxazin in the APVMA Adverse Experience Reporting Program database (AERP)[82].

International regulations

As of December 2021, flumioxazin is:

- In a summary document provided by the United States Environmental Protection Agency's (US EPA) Office of Pesticides Programs[83] database, flumioxazin is classified as possessing "mild or low toxicity" by oral, dermal and inhalational routes, and is not an irritant or sensitiser to the eye or skin.
- Listed in the European Commission database for information on cosmetic substances and ingredients (CosIng) database[84] as a reproductive toxin.
- Included in The New Zealand Inventory of Chemicals (NZIoC)[85].
- Included in the European Chemicals Agency (ECHA)[86] database as a suspected reproductive toxin.

[75] TGA Ingredient Database https://www.ebs.tga.gov.au/
[76] ARTG database https://www.tga.gov.au/artg
[77] Therapeutic Goods (Permissible Ingredients) Determination
https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[78] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[79] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[80] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[81] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[82] APVMA Adverse Experience Reporting Program database (AERP) https://apvma.gov.au/node/10946
[83] United States Environmental Protection Agency's (US EPA) Office of Pesticides Program
[84] European Commission database for information on cosmetic substances and ingredients database
[85] New Zealand Inventory of Chemicals (NZIoC) www.epa.govt.nz/database-search/new-zealand-inventory-of-chemicals
[86] European Chemicals Agency (ECHA) echa.europa.eu/search-for-chemicals

4.2 Flumioxazin (second private application)

Proposal

The applicant to the Australian Pesticides and Veterinary Medicines Authority (APVMA) has proposed that a new Schedule 5 entry be created for all formulations of flumioxazin except for water soluble bags individually packed in sealed sachets, which would be exempt from scheduling. The existing entries for flumioxazin in Schedules 6 and 7 would be deleted. The scheduling changes would increase access to flumioxazin for use as a herbicide.

CAS Number:

103361-09-7

Alternative names

2-[7-Fluoro-3,4-dihydro-3-oxo-4-(2-propyn-1-yl)-2*H*-1,4-benzoxazin-6-yl]-4,5,6,7-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione; *N*-(7-fluoro-3,4-dihydro-3-oxo-4-prop-2-ynyl-2*H*-1,4-benzoxazin-6-yl)cyclohex-1-ene-1,2-dicarboximide

Applicant

Private applicant (via APVMA)

Current scheduling

Flumioxazin is currently listed in Schedules 6 and 7 of the Poisons Standard as follows:

Schedule 7

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

Schedule 6

FLUMIOXAZIN when contained in water soluble bags individually packed in sealed sachets.

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FLUMIOXAZIN

Schedule 7
Schedule 6

Proposed scheduling

Schedule 7 – Delete Entry

~~FLUMIOXAZIN **except** when included in Schedule 6.~~

Schedule 6 – Delete Entry

~~FLUMIOXAZIN when contained in water soluble bags individually packed in sealed sachets.~~

Schedule 5 – New Entry

FLUMIOXAZIN **except** when contained in water soluble bags packed in sealed sachets.

Index – Amend Entry

FLUMIOXAZIN

~~Schedule 7~~
~~Schedule 6~~
Schedule 5

Background

- Flumioxazin is used as a herbicide in registered pesticide products for control of various grass and broadleaved weeds.
- In October 2002 flumioxazin was included in Schedule 7 of the Poisons Standard without any cut-off because of: irreversible developmental/reproductive effects observed at non-maternotoxic acute doses, chronic hepatotoxicity and induction of porphyria and the potential for photo dermatitis.
- In September 2011 the Schedule 7 entry for flumioxazin was amended to include a cut-off to Schedule 6 for preparations in water soluble bags when individually packed in sealed sachets.

Application summary - reasons for proposal

- Formulations containing flumioxazin are of low acute oral toxicity (in rats), low dermal and moderate acute inhalational toxicity, and are a slight eye and skin irritant in rabbits but are not a skin sensitiser.
- The potential respiratory irritation is not of concern when the product is contained in water soluble packaging, likewise for eye and skin irritation when handling the product during mixing and loading activities.
- The repeat dose toxicity data indicate that flumioxazin is unlikely to be genotoxic *in vivo*, and it is unlikely to be carcinogenic in humans under normal conditions of use. Developmental toxicity was observed in rats at non-maternally toxic doses, and there was no evidence of reproductive toxicity. The applicant submitted additional mechanistic data as part of a mode of action analysis to propose that the adverse rat developmental findings be dismissed as irrelevant to humans on the basis that the rat is not a suitable model. Experimental data shows that rats are particularly sensitive to the effects of protoporphyrinogen oxidase (PPO) inhibition induced by flumioxazin in erythroblasts. This leads to anaemia that is a critical precursor of the developmental toxicity resulting from flumioxazin exposure. The conclusion that humans are unlikely to develop anaemia from PPO inhibition is based on:
  - A species difference between rat and human in the erythropoiesis pattern during development.
  - Experimental evidence that flumioxazin does not reduce haem synthesis in K562 cells and CD36+ cells, which are derived from human erythroleukemia and human cord blood, respectively, nor in human induced pluripotent stem cells (hiPSCs).

- The absence of developmental effects in humans at therapeutic doses even though haem synthesis is inhibited in vitro in human K562 cells, CD36+ cells and hiPSCs.
- Experimental evidence that humans are less sensitive to PPO inhibition than rats.
- Clinical findings that PPO deficient patients with Variegate Porphyria (VP) show no signs of anaemia. There are no reports of cardiac malformation in VP patients or their babies.

Key uses / expected use

Agriculture

Australian and international regulations

Refer to 2.1 Flumioxazin (private application).

5 How to respond

Submissions must be provided by the closing date of **31 January 2022** 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.

6 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 **June 2022**.