Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Consultation: Proposed amendments to the Poisons Standard – ACMS, ACCS and Joint ACMS-ACCS meetings, March 2024

5 January 2024

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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 2024** meetings of the Advisory Committee on Medicines Scheduling (ACMS #44), Advisory Committee on Chemicals Scheduling (ACCS #38) and Advisory Committees on Medicines and Chemicals Scheduling in joint session (Joint ACMS-ACCS #36). Submissions must be received by close of business **5 February 2024**.

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 5 February 2024.

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

1 Proposed amendment referred for scheduling advice to ACMS meeting #44

1.1 Cytisine

Proposal

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

CAS number

485-35-8

Alternative names

Baptitoxine

Cytisinicline

Sophorine

Ulexine

(1*R*,5*S*)-1,2,3,4,5,6-Hexahydro-1,5-methano-8*H*-pyrido-[1,2-*a*][1,5]diazocin-8-one

Applicant

Private applicant

Proposed Scheduling

Cytisine is not specifically scheduled in the current Poisons Standard.

The applicant's proposed amendments to the Poisons Standard are[1]:

Schedule 4 – New Entry

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

Schedule 2 – New Entry

CYTISINE in divided preparations for oral use containing 1.5 mg or less of cytisine per dosage unit.

Index – New Entry

CYTISINE

Schedule 4
Schedule 2

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

Background

Cytisine is a plant-derived product that can be used as a smoking cessation aid to reduce nicotine withdrawal symptoms, and is proposed to be used as oral tablets for a 25 day course of treatment. Cytisine is not listed in the Poisons Standard and has not been previously considered for scheduling.

Summary of applicant's reasons for the proposal

- Tobacco smoking is the leading cause of preventable death and disability in Australia. Reducing harm from tobacco is a high priority in Australia to reduce illness, increase quality of life, save healthcare costs, and reduce health and economic inequalities for smokers.
- Nicotine dependence is a self-identifiable condition and can be self-managed with nicotine replacement therapy (NRT), which is available without a prescription. Cytisine is an alternative to NRT to aid smoking cessation and has comparable efficacy to varenicline (Champix), a prescription medicine indicated for smoking cessation.
- The classification of cytisine as a Schedule 2 (Pharmacy Only) medicine will enable more treatment options for smoking cessation be available to consumers, which is likely to have public health benefits for Australia. Being a Schedule 2 medicine, the availability of a pharmacist may also provide guidance for patients when required.
- Cytisine has been available for smoking cessation for over 50 years in Central and Eastern European countries. It is currently available without a prescription in these countries, and it is also available as a non-prescription natural product in Canada.

Key uses / expected use

Medicines

Australian regulations

- According to the TGA Ingredient Database, cytisine is:
  - Not available as an Active Ingredient in any application
  - Not available as an Excipient Ingredient in any application
  - Available for use as an Equivalent Ingredient in Export Only and Over the Counter medicines
- As of December 2023, there were no medicines active on the Australian Register of Therapeutic Goods (ARTG) that contain cytisine as an active ingredient.
- Cytisine is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination No.4 of 2023.
- Cytisine is not included in the TGA prescribing medicines in pregnancy database.
- There are no warning statements pertaining to cytisine in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.
- As of December 2023, there were 3 reports of adverse events for products containing cytisine as an active ingredient on the Database of Adverse Event Notifications (DAEN). For all three cytisine was the single suspected medicine. There were no reports of deaths associated with cytisine use.
- As of December 2023, there were no products containing cytisine as an active ingredient/constituent or scheduled substance listed on the Public Chemical Registration Information System Search (PubCRIS).
- As of December 2023, cytisine is not listed on the Australian Inventory of Industrial Chemicals.

International regulations

- Cytisine is not found in the US FDA database, New Zealand's Medsafe database, or the UK electronic medicines compendium (emc).
- The Ireland Health Products Regulatory Authority has approved one product containing cytisine as an active ingredient. This product is in tablet form (1.5 mg) and is available with a prescription.
- Cytisine is approved as a natural health product in Canada.
- Cytisine is available as a non-prescription medicine in Austria, Poland, Latvia and Portugal.

In response to a private application to up-schedule the opioid cough suppressant dihydrocodeine, the Delegate of the Secretary of the Department of Health and Aged Care that is responsible for medicines scheduling is proposing to up-schedule dextromethorphan and ethylmorphine. These substances are also available for use in over-the-counter cough and cold preparations, but may present similar concerns regarding their misuse and potential for abuse as identified for dihydrocodeine.

1.2 Dextromethorphan

Proposal

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

CAS number

125-71-3

Alternative names

DXM

Proposed Scheduling

The Delegate's proposed amendments to the Poisons Standard are[2]:

Schedule 4 – Amend Entry

DEXTROMETHORPHAN (excluding its stereoisomers) **except** when included in Schedule ~~2~~3.

Schedule 3 – New Entry

DEXTROMETHORPHAN (excluding its stereoisomers) when supplied in a pack containing 600 mg or less of dextromethorphan and with a recommended daily dose of 120 mg or less of dextromethorphan.

Schedule 2 – Delete Entry

~~DEXTROMETHORPHAN (excluding its stereoisomers) when supplied in a pack containing 600 mg or less of dextromethorphan and with a recommended daily dose of 120 mg or less of dextromethorphan.~~

Index – Amend Entry

DEXTROMETHORPHAN

Schedule 4
Schedule 3
~~Schedule 2~~

Appendix H, clause 1 – New Entry

DEXTROMETHORPHAN

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

Background

Dextromethorphan is a cough suppressant that is usually presented in capsules and oral liquids. When taken at doses that significantly exceed therapeutic recommendations, dextromethorphan can act as a dissociative hallucinogen and, therefore, products containing this substance present with a potential for abuse.

Summary of reasons for the proposal

- Low-dose preparations of dextromethorphan are available as Schedule 2 (pharmacy medicine) products for relief from persistent, dry coughs. However, due to the ongoing suspected abuse of dextromethorphan, there are several unconfirmed reports of pharmacists voluntarily placing these products “behind the counter” and requiring consumers to consult with a pharmacist prior to purchase.
- The Delegate has received an application to amend the Poisons Standard to delete the current Schedule 3 (Pharmacist only) entry for dihydrocodeine (see below). The proposal would move cough suppression preparations containing dihydrocodeine currently available as Schedule 3 (Pharmacist Only) medicines to Schedule 4 (Prescription Only). If dihydrocodeine becomes a prescription-only medicine, misusers of that substance may elect to switch to the more freely available dextromethorphan increasing the risk of its abuse.
- Dextromethorphan products are not available for self-selection in many comparable international jurisdictions.

Key uses / expected use

Medicines

Australian regulations

- According to the TGA Ingredient Database, dextromethorphan (as anhydrous or hydrobromide monohydrate) 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 December 2023, there were 55 medicines active on the Australian Register of Therapeutic Goods (ARTG) that contain dextromethorphan as an active ingredient. These include 54 non-prescription medicines and one export only medicine.
- Dextromethorphan is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination No.4 of 2023.

- The TGA prescribing medicines in pregnancy database classifies dextromethorphan as:

Drug name	Category	Safety statement	Classification Level 1	Classification Level 2	Classification Level 3
Dextromethorphan	A		Respiratory System	Antitussives	
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 2021 requires the following warning statements pertaining to dextromethorphan to be included on the labelling:

Substance	Circumstances	Required Statements
Dextromethorphan (Entry 1 of 2)	In oral preparations indicated for cough, cold or flu which DO NOT include dosage instructions for children aged under 12 years	Do not give to children under 12 years of age. If [coughing/symptoms] persist(s), consult your doctor or pharmacist
Dextromethorphan (Entry 2 of 2)	In oral preparations indicated for cough, cold or flu which include dosage instructions for children aged from 'x' to 11 years (where 'x' is 6, 7, 8, 9, 10 or 11)	Do not give to children under 'x' years of age. *either (if 'x' is 11)* Do not give to children aged 11 years, except on the advice of a doctor, pharmacist or nurse practitioner. *or (if 'x' is 6, 7, 8, 9 or 10)* Do not give to children aged between 'x' and 11 years of age, except on the advice of a doctor, pharmacist or nurse practitioner. If [coughing/symptoms] persist(s), consult your doctor or pharmacist.

- Between January 2013 and December 2023, there were 48 reports of adverse events for products containing dextromethorphan as an active ingredient on the Database of Adverse Event Notifications (DAEN), with 34 reports where dextromethorphan was the single suspected medicine. There were 4 deaths associated with use of dextromethorphan. Reported events were diverse in nature and affected various organ classes.
- As of December 2023, there was one product containing dextromethorphan as an active ingredient/constituent or scheduled substance listed on the Public Chemical Registration Information System Search (PubCRIS).
  - The product is a cough mixture for the treatment and relief of respiratory illnesses in cats and dogs, available by prescription only.

- In 2010-2020 the following adverse experiences were recorded for dextromethorphan in the APVMA Adverse Experience Reporting Program database (AERP):
  - 2 reports of incidents classified as related to animal health (2015 and 2019-20).
- As of December 2023, dextromethorphan is not listed on the Australian Inventory of Industrial Chemicals.

International regulations

- The Health Canada Drug Product Database includes 116 marketed products containing dextromethorphan. All are available as over-the-counter medicines.
- The New Zealand Medsafe Medicines Classification Database lists dextromethorphan as follows:

Ingredient	Conditions (if any)	Classification
Dextromethorphan	**except** when specified elsewhere in this schedule	Prescription
Dextromethorphan	in liquid form when in packs containing not more than 600 milligrams and with a recommended daily dose of not more than 120 milligrams; in medicines for the treatment of symptoms of cough and cold in adults and children aged 6 years and over	Restricted

- The US Food and Drug Administration's Orange Book includes 33 approved drug products containing dextromethorphan. These include 16 prescription-only medicines and 17 over-the-counter medicines. All OTC medicines containing dextromethorphan are extended-release tablets or extended-release suspensions.
- Ireland's Health Products Regulatory Authority regulates 6 products containing dextromethorphan. All are available for supply through pharmacies only.

1.3 Dihydrocodeine

Proposal

The applicant has proposed to delete the current Schedule 3 entry for dihydrocodeine from the Poisons Standard. The proposal would move cough suppression preparations containing dihydrocodeine that are currently available as Schedule 3 (Pharmacist Only) medicines to Schedule 4 (Prescription Only).

CAS number

125-28-0

Alternative names

(5α,6α)-4,5-Epoxy-3-methoxy-17-methylmorphinan-6-ol; 6-hydroxy-3-methoxy-*N*-methyl-4,5-epoxymorphinan

Dihydroneopine

Applicant

Private applicant

Proposed Scheduling

The applicant's proposed amendments to the Poisons Standard are[3]:

Schedule 8 – Amend Entry

DIHYDROCODEINE **except** when included in Schedule ~~3 or~~ 4**.**

Schedule 4 – Amend Entry

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

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

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

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

Schedule 3 – Delete Entry

~~DIHYDROCODEINE when indicated for cough suppression and compounded with one or more other therapeutically active substances:~~

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

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

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

Index – Amend Entry

DIHYDROCODEINE

Schedule 8
Schedule 4
~~Schedule 3~~
Appendix K, clause 1

Appendix K, clause 1

Human medicines required to be labelled with a sedation warning

Item	Poison
45	DIHYDROCODEINE

Background

Dihydrocodeine is an opioid derivative that is used to relieve dry coughs and to treat moderate to moderately severe pain. Dihydrocodeine has a high risk of dependence even when taken at therapeutic doses. It can also produce euphoria and has a known potential for abuse. As an opioid, the use of dihydrocodeine is associated with the risk of respiratory depression, tolerance, physical dependence and withdrawal.

Dihydrocodeine is available as a Schedule 3 (Pharmacist Only) oral liquid for the relief of stubborn unproductive cough. There is currently one registered product containing dihydrocodeine that is available as a pharmacist only medicine in Australia.

The scheduling of dihydrocodeine was considered alongside the up-scheduling of codeine in 2016, which became a prescription-only medicine in February 2018. Dihydrocodeine was last considered in 2017, where the Schedule 2 entry that included products co-formulated with aspirin was deleted, and the Schedule 3 entry was retained due to lack of evidence to support its deletion.

Summary of applicant's reasons for the proposal

- Dihydrocodeine is a highly addictive substance and is commonly sought out by the public for recreational use or off label management of opioid addiction.
- The current formulation of Schedule 3 (Pharmacist Only) dihydrocodeine preparation contains sorbitol which aims to limit potential abuse by exerting unwanted gastrointestinal side effects if daily dose is exceeded. However, this combination does not prevent misuse or overuse of the product.
- Pharmacy settings are unable to control the supply of dihydrocodeine to consumers as other members of the public can purchase products on their behalf.

Key uses / expected use

Medicines

Australian regulations

- According to the TGA Ingredient Database, dihydrocodeine 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 December 2023, there was one medicine active on the Australian Register of Therapeutic Goods (ARTG) that contain dihydrocodeine as an active ingredient.
- Dihydrocodeine is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination No.4 of 2023.
- The TGA prescribing medicines in pregnancy database classifies dihydrocodeine as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Dihydrocodeine	A	Central Nervous System	Analgesics and Antipyretics (see also non-steroidal anti-inflammatory agents)	Opioid analgesics
Dihydrocodeine	A	Respiratory System	Antitussives	
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 2021 requires the following warning statements pertaining to dihydrocodeine to be included on the labelling:

Substance	Conditions	Required Statement(s)
Dihydrocodeine	In oral preparations indicated for cough, cold or flu which DO NOT include dosage instructions for children aged under 12 years	Do not give to children under 12 years of age. If [coughing/symptoms] persist(s), consult your doctor or pharmacist.
Dihydrocodeine	In oral preparations indicated for cough, cold or flu which include dosage instructions for children aged from 'x' to 11 years (where 'x' is 6, 7, 8, 9, 10 or 11)	Do not give to children under 'x' years of age. *either (if 'x' is 11)* Do not give to children aged 11 years, except on the advice of a doctor, pharmacist or nurse practitioner. *or (if 'x' is 6, 7, 8, 9 or 10)* Do not give to children aged between 'x' and 11 years of age, except on the advice of a doctor, pharmacist or nurse practitioner. If [coughing/symptoms] persist(s), consult your doctor or pharmacist.

- From January 2013 to December 2023, there were 39 reports of adverse events for products containing dihydrocodeine as an active ingredient on the Database of Adverse Event Notifications (DAEN), with 31 reports where dihydrocodeine was the single suspected medicine. There were 3 reports of deaths associated with dihydrocodeine use. 32 of the adverse events reported in that period occurred after 1 February 2018, when codeine was re-scheduled as a prescription-only medicine.

- As of December 2023, there were no products containing dihydrocodeine as an active ingredient/constituent or scheduled substance listed on the Public Chemical Registration Information System Search (PubCRIS).
- As of December 2023, dihydrocodeine is not listed on the Australian Inventory of Industrial Chemicals.

International regulations

- According to the United States Food and Drug Administration Approved Drug Products Database (Drugs@FDA), there is currently 1 product in the form of capsules/tablets that contain dihydrocodeine as an active ingredient, which is in combination with acetaminophen (paracetamol) and caffeine. This product is a prescription only medicine.
- According to New Zealand's Medsafe, dihydrocodeine is variously classified as a prescription medicine, a Class C6 controlled drug (limits on dosage and concentration) and Class C2 controlled drug.
- No medicines containing dihydrocodeine were included in the Canadian (Health Canada) Drug Product Database.
- According to the electronic medicines compendium (emc), there are currently 4 products available in the United Kingdom that are indicated for the relief of pain that contain dihydrocodeine as a single substance or in combination with paracetamol. All of these are prescription medicines, except for a paracetamol (500 mg) and dihydrocodeine tartrate (7.5 mg) combination product which is available as a pharmacy only medicine.
- Ireland's Health Products Regulatory Authority (HPRA) regulates 3 products that contain dihydrocodeine as an active ingredient for the treatment of non-productive cough. All are prescription medicines.

1.4 Ethylmorphine

Proposal

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

CAS number

76-58-4

Alternative names

Codethyline

Dionine

Proposed Scheduling

The Delegate's proposed amendments to the Poisons Standard are[4]:

Schedule 8 – Amend Entry

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

Schedule 4 – Amend Entry

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

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

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

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

Schedule 2 – Delete Entry

~~ETHYLMORPHINE when:~~

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

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

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

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

Index – Amend Entry

ETHYLMORPHINE

Schedule 8
Schedule 4
~~Schedule 2~~

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

Background

Ethylmorphine is an opioid analgesic that has previously been available over-the-counter in low-dose oral solutions as a cough suppressant. While there are currently no registered OTC products containing ethylmorphine, under the existing scheduling some preparations of ethylmorphine can still be imported, or used in compounded medicines, for cough suppression without requirement for a prescription.

Summary of reasons for the proposal

The current Schedule 2 entry for ethylmorphine is a legacy entry that has not been considered by a scheduling committee since the early 1990s. As outlined in the proposal for dihydrocodeine (see above), it may not be appropriate for any opioid to be available to patients without oversight from a pharmacist or doctor, due to the associated risks of dependence, potential for abuse and respiratory depression.

Key uses / expected use

Medicines

Australian regulations

- According to the TGA Ingredient Database, ethylmorphine (as hydrochloride dihydrate) 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 December 2023, there were no medicines active on the Australian Register of Therapeutic Goods (ARTG) that contain ethylmorphine as an active ingredient.
- Ethylmorphine is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination No.4 of 2023.
- The TGA prescribing medicines in pregnancy database does not include ethylmorphine.
- There are no warning statements pertaining to ethylmorphine in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.
- As of December 2023, there were 2 reports of adverse events for products containing ethylmorphine as an active ingredient on the Database of Adverse Event Notifications (DAEN), with one report where ethylmorphine was the single suspected medicine. There were no reports of death associated with ethylmorphine use.
- As of December 2023, there were no products containing ethylmorphine as an active ingredient/constituent or scheduled substance listed on the Public Chemical Registration Information System Search (PubCRIS).
- As of December 2023, ethylmorphine is not listed on the Australian Inventory of Industrial Chemicals.

International regulations

- Ethylmorphine is not listed on the Health Canada Drug Product Database.
- Ethylmorphine is listed on New Zealand's Medsafe Classification Database as follows:

Ingredient	Conditions (if any)	Classification
Ethylmorphine	Other than a preparation or mixture described in Schedule 3, Part 6.	Class C3 Controlled Drug
Ethylmorphine	(i) Compounded with one or more other pharmacologically active ingredients in such a way that the substance cannot be recovered by readily applicable means or in a yield which would constitute a risk to health; and (ii) Containing not more than 100 milligrams of the substance in each dosage unit and with a concentration of not more than 2.5 percent in undivided preparations.	Class C6 Controlled Drug

- Ethylmorphine is not included on the FDA's Approved Drugs Database. Ethylmorphine is a Schedule II controlled substance in the United States under the Controlled Substances Act.

2 Proposed amendments referred for scheduling advice to ACCS meeting #38

2.1 Ethyl lactyl retinoate

Proposal

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

CAS Number

74534-80-8

Alternative names

Retinoic acid, 2-ethoxy-1-methyl-2-oxoethyl ester

Applicant

Private applicant

Proposed Scheduling

The applicant has proposed amendments to the Poisons Standard as follows:

Schedule 4

TRETINOIN except:

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

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

Current Scheduling

Ethyl lactyl retinoate is not specifically scheduled in the current Poisons Standard, but may be captured as a derivative of TRETINOIN:

Schedule 4

TRETINOIN **except** the ester hydroxypinacolone retinoate in preparations for dermal use containing 0.5% or less of hydroxypinacolone retinoate.

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TRETINOIN

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

It may also be included under the entries for TRETINOIN in Appendices D and F as follows:

Appendix D, clause 4 (Poisons only available from or on the order of a specialist physician)

TRETINOIN for human oral use

Appendix F, clause 4

Item	Poison	Warning statement
343	TRETINOIN – for human oral use	**7** – WARNING – Causes birth defects
		62 – Do not use if pregnant
		76 – Do not become pregnant during use or within (Insert number of months as per approved Product Information) month(s) of stopping treatment
344	TRETINOIN – for topical use	**62** – Do not use if pregnant
		77 – WARNING – May cause birth defects

Background

Ethyl lactyl retinoate is an ester of tretinoin that, under the provision for derivatives in the Poisons Standard, may be captured by the Schedule 4 entry for that substance. Ethyl lactyl retinoate has potential for use in cosmetic preparations as it may have several beneficial effects on the skin. The substance has been suggested as a safer and better tolerated option than several other retinoids for this purpose.

Summary of applicant's reasons for the proposal

- Ethyl lactyl retinoate does not hydrolyse in vivo to retinoic acid and its binding to retinoid receptor is sterically hindered. Both of these factors contribute to the greatly enhanced safety profile of ethyl lactyl retinoate when compared to substances such as tretinoin and retinoic acid.
- ethyl lactyl retinoate has demonstrated lower potential for causing dermal irritation than other retinoids, illustrating the safety of its use as a dermal cosmetic ingredient at the low concentrations specified in this proposal.
- The substance has a similar safety profile to hydroxypinacolone retinoate, which was exempted from the scheduling entry for tretinoin on 1 February 2023.

Key uses / expected use

Cosmetics

Australian regulations

- Ethyl lactyl retinoate is not included in the TGA Ingredient Database or any products in the Australian Register of Therapeutic Goods (ARTG).
- Ethyl lactyl retinoate is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination No.4 of 2023.
- Ethyl lactyl retinoate is not included in the TGA prescribing medicines in pregnancy database.
- There are no warning statements pertaining to ethyl lactyl retinoate in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.
- As of December 2023, there were no reports of adverse events for products containing ethyl lactyl retinoate as an active ingredient on the Database of Adverse Event Notifications (DAEN).

- As of December 2023, there were no products containing ethyl lactyl retinoate as an active ingredient/constituent or scheduled substance listed on the Public Chemical Registration Information System Search (PubCRIS).
- Ethyl lactyl retinoate is not listed on the Australian Inventory of Industrial Chemicals.

International regulations

- Ethyl lactyl retinoate is included on the European Commission's CosIng database of cosmetic ingredients as an abrasive and skin conditioner.
- Ethyl lactyl retinoate is not present on the databases of the European Chemicals Agency, United States Environmental Protection Agency, or New Zealand Inventory of Chemicals (NZIoC).
- Ethyl lactyl retinoate is not present in the FDA's Approved Drugs database, New Zealand Medsafe's Medicines Classification Database, or Health Canada's Drug Product Database.

2.2 Niclosamide

Proposal

The applicant proposed to create a Schedule 5 entry for niclosamide when in tablet or paste preparations for companion animals, and a Schedule 6 entry for niclosamide except when included in Schedule 2 or 5.

CAS Number:

50-65-7

Alternative names

5-Chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide

N-(2′-chloro-4′-nitrophenyl)-5-chlorosalicylamide

2',5-dichloro-4'-nitrosalicylanilide

Applicant

Australian Pesticides and Veterinary Medicines Authority (APVMA)

Proposed Scheduling

The applicant's proposed amendments to the Poisons Standard are:[5]

Schedule 6 – New entry

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

Schedule 5 – New entry

NICLOSAMIDE in tablet or paste preparations for companion animals.

Schedule 2

NICLOSAMIDE for human therapeutic use.

Index – Amend Entry

NICLOSAMIDE

Schedule 6
Schedule 5
Schedule 2

Background

Niclosamide is an anthelmintic medication used to treat parasitic infections in humans and animals. At present, niclosamide is available in veterinary products as an oral worming treatment in dogs and cats. Niclosamide has been widely used overseas to control aquatic (freshwater) snails. However, it has not previously been used in agriculture in Australia. Recently an emergency permit was issued to control rice snails (PER93840, 2023).

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

Niclosamide for human therapeutic use is included in Schedule 2 of the Poisons Standard. However there are presently no products for human therapeutic use listed on the ARTG that contain niclosamide.

Summary of applicant's reasons for the proposal

Niclosamide is a molluscicide and anthelmintic that has a significant history of use for the control of parasites in both human and veterinary settings. While there are already unscheduled niclosamide products marketed in Australia for use in cats and dogs, an application for use of the substance in a new molluscicide product has prompted this proposal to include such use in the Poisons Standard.

Key uses / expected use

Medicines, veterinary, and agriculture

Australian regulations

- According to the TGA Ingredient Database, niclosamide is:
  - Available for use as an Active Ingredient in: Biologicals, 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 2023, there were no medicines active on the Australian Register of Therapeutic Goods (ARTG) that contain niclosamide as an active ingredient.
- Niclosamide is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination No.4 of 2023
- Niclosamide is not listed in the TGA prescribing medicines in pregnancy database.
- There are no warning statements pertaining to niclosamide in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.
- As of December 2023, there were 3 reports of adverse events for products containing niclosamide as an active ingredient on the Database of Adverse Event Notifications (DAEN), with 1 report where niclosamide was the single suspected medicine. There were no reports of deaths associated with niclosamide use.
- As of December 2023, there were 13 products containing niclosamide as an active ingredient/constituent or scheduled substance listed on the Public Chemical Registration Information System Search (PubCRIS). These include oral tablets and oral pastes for animal use.
- In 2015-2020 the following adverse experiences were recorded for niclosamidein the APVMA Adverse Experience Reporting Program database (AERP):
  - 1 report of a serious incident classified as related to animal health reported (2018-2019).
- As of December 2023, niclosamide is listed on the Australian Inventory of Industrial Chemicals.

International regulations

- According to the European Chemicals Agency (ECHA), niclosamide causes serious eye irritation, and is very toxic to aquatic life, and very toxic to aquatic life with long lasting effects.
- Niclosamide is not listed in the EU Pesticides database.
- In Canada, there are currently 4 products containing niclosamide listed in the Pesticide Product Information Database. Niclosamide is not listed in the Health Canada Drug Product Database.

- In New Zealand, niclosamide is listed on the Inventory of Chemicals without individual approval but may be used under an appropriate group standard. New Zealand Medsafe classifies niclosamide as a pharmacy only medicine.

3 Proposed amendments referred for scheduling advice to the Joint ACMS-ACCS meeting #36

2.3 Oxytetracycline

Proposal

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

CAS Number

79-57-2

Alternative names

Hydroxytetracycline

Applicant

Private applicant

Proposed Scheduling

The applicant's proposed amendments to the Poisons Standard are[6]:

Schedule 5 – Amend Entry

OXYTETRACYCLINE in preparations:

a) for topical application to animals:

(i) for ocular use ~~only~~; or
(ii) to treat superficial skin infections; or

b) containing 40% or less of oxytetracycline per dose, when packed and labelled for the treatment of ornamental caged birds or ornamental fish only.

Schedule 4

OXYTETRACYCLINE **except** when included in Schedule 5.

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OXYTETRACYCLINE

Schedule 5
Schedule 4

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

Background

Oxytetracycline is a broad-spectrum antibiotic that belongs to the tetracycline drug class. The substance can be used for the treatment of bacterial infections in humans. However, in Australia use of oxytetracycline is currently limited to veterinary settings. The application seeks to make topical preparations of oxytetracycline for veterinary use available without requiring a prescription.

Summary of applicant's reasons for the proposal

- Oxytetracycline is a broad-spectrum bacteriostatic antibiotic that is effective against a wide range of Gram-positive and Gram-negative bacteria. Direct access to oxytetracycline benefits farmers when they do not have veterinarian access and could serve as a first line defence against superficial infections.
- Topical veterinary applications of oxytetracycline are used in the treatment of foot rot in sheep, digital dermatitis in cattle and superficial skin infections caused by oxytetracycline sensitive organisms in pigs, sheep and cattle.
- Topical oxytetracycline absorption is negligible and the drug acts via direct contact with bacteria on the skin and in superficial lesions on external body surfaces.
- Topical oxytetracycline formulations can achieve a nil meat and milk withhold.
- Oxytetracycline is not considered to present a significant risk in the development of antimicrobial resistance in the treatment of infections in humans. Oxytetracycline are used in human therapeutics and are classed as antibiotics of low importance.
- Allergic reactions to any residues of oxytetracycline are not expected to occur.
- The toxicity, teratogenicity and carcinogenicity of topical formulations are deemed low to no risk.

Key uses / expected use

Medicines, veterinary medicines

Australian regulations

- Oxytetracycline is not listed on the TGA Ingredient Database.
- As of 15 December 2023, there were no medicines active on the Australian Register of Therapeutic Goods (ARTG) that contain oxytetracycline as an active ingredient.
- Oxytetracycline is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination No.4 of 2023.
- The TGA prescribing medicines in pregnancy database classifies oxytetracycline as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Oxytetracycline	D	Antimicrobials	Antibiotics	Tetracyclines
Category D – Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.				

- The are no warning statements pertaining to oxytetracycline in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.
- As of December 2023, there were 17 reports of adverse events for products containing oxytetracycline as an active ingredient on the Database of Adverse Event Notifications (DAEN),

with 13 reports where oxytetracycline was the single suspected medicine. There were no reports of deaths associated with oxytetracycline use.

- As of December 2023, there were 73 products containing oxytetracycline as an active ingredient/constituent or scheduled substance listed on the Public Chemical Registration Information System Search (PubCRIS).
- In 2010-2020 the following adverse experiences were recorded for oxytetracycline in the APVMA Adverse Experience Reporting Program database (AERP):
  - 2 reports of serious incidents classified as related to animal health reported in the 2018/2019 financial year.
  - 1 report of a serious incident classified as related to animal health reported in 2011.
  - 3 reports of serious incidents classified as related to animal health reported in 2009.
- As of December 2023, oxytetracycline is not listed on the Australian Inventory of Industrial Chemicals.

International regulations

- The United States Environmental Protection Agency's (US EPA) Office of Pesticides Programs list oxytetracycline hydrochloride under reregistration.
- According to the classification provided by companies to the European Chemicals Agency (ECHA) in classification, labelling and packaging (CLP) notifications, oxytetracycline is very toxic to aquatic life with long lasting effects, is very toxic to aquatic life, may damage fertility or the unborn child, is harmful if swallowed, is harmful in contact with skin, is harmful if inhaled, is suspected of damaging fertility or the unborn child, causes serious eye irritation, may cause harm to breast-fed children, may cause an allergic skin reaction, causes skin irritation and may cause respiratory irritation.
- The New Zealand Inventory of Chemicals (NZIOC) lists oxytetracycline compounds as does not have an individual approval but may be used under an appropriate group standard.
- The Canada's Pest Management Regulation Agency does not list oxytetracycline.
- The United States Food and Drug Administration Approved Drug Products Database (Drugs@FDA) includes 14 discontinued products containing oxytetracycline.
- The New Zealand Medsafe Medicines Classification Database lists oxytetracycline as a prescription medicine.
- The Health Canada Drug Product Database includes 15 marketed products containing oxytetracycline. All are available for supply as prescription and classed as veterinary products.

2.4 Tranexamic acid

Proposal

The applicant proposed exemption of topical cosmetic preparations containing up to 3% tranexamic acid from the Schedule 4 entry for the substance. At present, the scheduling exemption is limited to the derivative cetyl tranexamate.

CAS number

1197-18-8

Alternative names

Cyclohexanecarboxylic acid, 4-(aminomethyl)-, trans-

TXA

Applicant

Private applicant

Proposed Scheduling

The applicant's proposed amendments to the Poisons Standard are:[7]

Schedule 4 – Amend Entry

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

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TRANEXAMIC ACID
cross reference: CETYL TRANEXAMATE

Schedule 4

Background

Tranexamic acid is used therapeutically as an intravenous injectable prior to dental extraction in patients with haemophilia to reduce risk of haemorrhaging, and orally in the treatment of heavy menstrual bleeding. It is also used in topical preparations up to a 3% concentration as a cosmetic skin conditioning agent to improve skin complexion. However, in Australia tranexamic acid products are only registered and marketed for therapeutic uses.

Summary of applicant's reasons for the proposal

- Tranexamic acid has a well-established safety profile in intravenous (IV) and oral preparations. Notably tranexamic has low acute oral toxicity and does not cause irritation to the eyes or skin, or skin sensitisation.
- Ocular toxicity has been reported in dogs at repeated high doses but would be negligible in the proposed dosage form.

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

- There is no risk of substance abuse or misuse at the proposed dosage and is highly unlikely to result in serious adverse effects.

Key uses / expected use

Medicines, cosmetics

Australian regulations

- According to the TGA Ingredient Database, tranexamic acid is:
  - Available for use as an Active Ingredient in: Biologicals, Export Only, Over the Counter, Prescription Medicines
  - Available for use as an Excipient Ingredient in: Biologicals, Devices, Export Only, Over the Counter, Prescription Medicines
  - Not available as an Equivalent Ingredient in any application
- As of December 2023, there were 27 medicines active on the Australian Register of Therapeutic Goods (ARTG) that contain tranexamic acid as an active ingredient. All registered medicines are prescription-only.
- Tranexamic acid is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination No. 4 of 2023.
- The TGA prescribing medicines in pregnancy database classifies tranexamic acid as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Tranexamic acid	B1	Cardiovascular System	Haemostatic agents	
Category B1 – 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 not shown evidence of an increased occurrence of foetal damage.				

- There are no warning statements pertaining to tranexamic acid in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.
- Between January 2013 and December 2023, there were 84 reports of adverse events for products containing tranexamic acid as an active ingredient on the Database of Adverse Event Notifications (DAEN), with 49 reports where tranexamic acid was the single suspected medicine. There were 3 reports of deaths associated with tranexamic acid use. The reported events were varied in nature and affected various organ classes.
- As of December 2023, there was one product containing tranexamic acid as an active ingredient/constituent or scheduled substance listed on the Public Chemical Registration Information System Search (PubCRIS).
- In 2010-2020 no adverse experiences were recorded for tranexamic acid in the APVMA Adverse Experience Reporting Program database (AERP).
- As of December 2023, tranexamic acid is not listed on the Australian Inventory of Industrial Chemicals.

International regulations

- In the USA, the FDA Drug Products Database lists tranexamic acid as available as a prescription-only medicine as an injectable (100 mg/mL), intravenous solution (10 mg/mL), and oral preparations (650 mg).
- The Health Canada Drug Product Database classifies tranexamic acid as a prescription-only medicine.
- The ECHA lists tranexamic acid as a 'GHS07: Health Hazard' with a CLP statement that the substance causes serious eye irritations, causes skin irritation and may cause respiratory irritation. In Europe, tranexamic acid is also listed as an astringent and skin conditioning cosmetic ingredient.
- Oral and injectable preparations of tranexamic acid are available as prescription-only medicines on the UK MHRA and Ireland's HPRA.
- The New Zealand Inventory of Chemicals lists tranexamic acid as Cyclohexanecarboxylic acid, 4-(aminomethyl)-, trans-, and does not have an individual approval but may be used as a component in a product covered by a group standard. It is not approved for use as a chemical in its own right.
- As a medicine, tranexamic acid is classified as a prescription medicine on the New Zealand Medicines and Medical Devices Safety Authority (MedSafe).

How to respond

Submissions must be provided by the closing date of **5 February 2024** 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.

What will happen

All public submissions will be published on the TGA website at public submissions on scheduling matters, unless marked confidential.

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 and furthers comments will be sought.

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