Australian Government
Department of Health
Therapeutic Goods Administration

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

29 April 2022

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 June 2022 meetings of the Advisory Committee on Medicines Scheduling (ACMS #38), Advisory Committee on Chemicals Scheduling (ACCS #34) and Joint Advisory Committee on Medicines and Chemicals Scheduling (Joint ACMS-ACCS #31). Submissions must be received by close of business **27 May 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 27 May 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 #38, June 2022

2.1 Cetirizine

Proposal

The applicant has proposed an amendment to the current Schedule 2 entry for cetirizine to lower the maximum age of patients for whom the substance is indicated, from 12 years and over to 6 years and over, when not scheduled in the Poisons Standard. The amended entry would allow access to certain oral preparations of cetirizine for the treatment of seasonal allergic rhinitis from outlets such as supermarkets for individuals aged 6 years and over.

CAS number

83881-52-1

Alternative names

[2-[4-(*p*-chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy]acetic acid; cetirizine hydrochloride

Applicant

Private applicant

Current scheduling

Schedule 4

CETIRIZINE **except**

a) when included in Schedule 2; or

b) in divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

i) in a primary pack containing not more than 10 days' supply; and

ii) labelled with a recommended daily dose not exceeding 10 mg of cetirizine.

Schedule 2

CETIRIZINE in preparations for oral use **except** in divided preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

a) in a primary pack containing not more than 10 days' supply; and

b) labelled with a recommended daily dose not exceeding 10 mg of cetirizine.

Appendix K – Drugs required to be labelled with a sedation warning

CETIRIZINE

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CETIRIZINE

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ANTIHISTAMINES

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

Schedule 4
Appendix F, Part 3

Proposed scheduling

Schedule 4 – Amend entry

CETIRIZINE **except**

a) when included in Schedule 2; or

b) in divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children ~~12~~6 years of age and over when:

i) in a primary pack containing not more than 10 days' supply; and

ii) labelled with a recommended daily dose not exceeding 10 mg of cetirizine.

Schedule 2 – Amend entry

CETIRIZINE in preparations for oral use **except** in divided preparations for the treatment of seasonal allergic rhinitis in adults and children ~~12~~6 years of age and over when:

a) in a primary pack containing not more than 10 days' supply; and

b) labelled with a recommended daily dose not exceeding 10 mg of cetirizine.

Background

Cetirizine hydrochloride (proprietary name Zyrtec, among others) is an orally active, second-generation H1-receptor antagonist used as a medicine to treat hay fever and allergy symptoms in children and adults. Cetirizine has been available in Australia since 1993, beginning as a Schedule 4 (prescription only) medicine and moving to Schedule 3 (Pharmacist Only Medicine) in 1997.

Application summary - reasons for proposal

- Cetirizine is for minor ailments or symptoms that can easily be recognised and treated by the consumer, and the risk profile of the substance in terms of potential for abuse and misuse is low. Quality use of the medicine can be achieved by labelling,

- Similar antihistamines such as fexofenadine and loratadine have previously been made available to the over 6-year age group in general sale.
- The application refers to a 5 mg chewable tablet form of cetirizine, which is currently under evaluation by the TGA and is the recommended solid oral dosage form for children aged 6-12 years.
- The applicant asserts that pharmacokinetic parameters (peak plasma levels, time to plasma peak) of oral cetirizine are similar for children 6-12 years old and adults, with slightly increased elimination rates in children.
- Seasonal allergic rhinitis (SAR) is a common and recognisable condition, which can follow a rapid and unpredictable course based on the presence of environmental allergens. However, treatment of SAR symptoms with cetirizine for children aged 6-12 years currently requires access to a pharmacy, which typically have restricted trading hours. Increased access to this substance by enabling availability to supermarkets and other retailers with extended trading would allow timely treatment of SAR symptoms in children.
- All medicines containing cetirizine are subject to pre-market approval by the Therapeutic Goods Administration (TGA), which will require appropriate warning statements and other safety information to be present on the product labelling. The applicant asserts that this will significantly mitigate safety concerns regarding abuse, misuse and medication error.
- Cetirizine for use in children 6 years and over has been available in general sale in several major western markets for well over a decade, including the USA, UK, Sweden and Netherlands. No concerns have been raised regarding the supply of cetirizine for children 6 years and above by regulators in these countries.
- Widening the use of unscheduled cetirizine to include children aged 6 to 12 years will increase the access of consumers to an appropriate divided dose cetirizine for more family members. This is in line with the TGA strategic framework and hence the Scheduling Framework, which seeks to provide healthcare that is affordable, accessible, efficient, and high quality without unnecessary regulatory burden.

Key uses / expected use

Medicine

Australian regulations

- Cetirizine (as hydrochloride) is listed as an ingredient on the TGA Ingredient Database[1].
  - 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; and
  - Not available as an equivalent ingredient in any application.
- As of April 2022, there were 64 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[2] that contain cetirizine as an active ingredient. All are non-prescription medicines.

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

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

- Cetirizine is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[3] No. 3 of 2022.
- The Therapeutic Goods (Medicines Advisory Statements) Specification 2021[4] requires the following warning statements in regard to cetirizine:

Substance	Circumstances	Required Statements
Cetirizine *(Entry 1 of 2)*	In preparations for oral use that are NOT specifically labelled for use only in children (between 1 year and 12 years of age)	*either* – This medication may cause drowsiness. If affected do not drive a vehicle or operate machinery. Avoid alcohol. *or* – This medication may cause drowsiness and may increase the effects of alcohol. If affected do not drive a motor vehicle or operate machinery. • If you are pregnant or breastfeeding, check with your doctor or pharmacist before using this medicine.
Cetirizine *(Entry 2 of 2)*	In preparations for oral use specifically labelled for use only in children (between 1 year and 12 years of age)	• This medication may cause drowsiness.

- Between January 1971 and April 2022, there were 250 reports of adverse events for products containing cetirizine as an active ingredient on the Database of Adverse Event Notifications (DAEN)[5]. 181 reports identified cetirizine as the single suspected medicine, and no reported deaths. The reactions reported were diverse in nature, with the most common being minor nervous system disorders such as somnolence, headache and dizziness.

[3] Therapeutic Goods (Permissible Ingredients) Determination No. 3 2022: https://www.legislation.gov.au/Details/F2022L00496
[4] Therapeutic Goods (Medicines Advisory Statements) Specification 2021: https://www.legislation.gov.au/Details/F2019L00213
[5] Database of Adverse Event Notifications (DAEN): https://apps.tga.gov.au/Prod/daen/daen-entry.aspx

- As of April 2022, there were no products containing cetirizine listed on the Public Chemical Registration Information System Search (PubCRIS).[6]
- The TGA prescribing medicines in pregnancy database[7] classifies cetirizine as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Cetirizine	B2	Allergy and immune system	Antihistamines	
Category B2 – 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.				

International regulations

- Cetirizine is not included in the WHO Model List of Essential Medicines 2019.[8]
- The Health Products Regulatory Authority of Ireland[9] regulates cetirizine as a non-prescription medicine but specifies "Supply through pharmacies only".
- The United States Food and Drug Administration[10] regulates cetirizine in tablets as an over-the-counter (non-prescription) medicine.
- The Canadian (Health Canada) Drug Product Database[11] lists cetirizine in 5mg and 10mg solid oral dosage forms as over-the-counter (non-prescription) medicines, with 20mg formulations restricted to prescription only.
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe),[12] oral dosage forms of cetirizine are available as both a Pharmacy Only and General Sale item, with the latter criteria being "in divided solid dosage forms for oral use containing 10 milligrams or less of cetirizine hydrochloride per dose form for the treatment of seasonal allergic rhinitis when sold in the manufacturer's original pack containing not more than 5 days' supply".

[6] Public Chemical Registration Information System Search (PubCRIS): https://portal.apvma.gov.au/pubcris
[7] TGA prescribing medicines in pregnancy database: https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[8] WHO Model List of Essential Medicines 2019: https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06
[9] Health Products Regulatory Authority of Ireland: https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/
[10] United States Food and Drug Administration: https://www.accessdata.fda.gov/scripts/cder/daf/
[11] Canadian (Health Canada) Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[12] New Zealand Medicines and Medical Devices Safety Authority (Medsafe): https://www.medsafe.govt.nz/profs/class/classintro.asp

2.2 Budesonide

Proposal

Creation of a Schedule 3 entry for inhaled budesonide in single ingredient inhaler devices for the maintenance of asthma in people aged 12 years and older where the maximum daily dose does not exceed 800 micrograms. Inhaled formulations of budesonide are currently available only with a prescription.

CAS number

51333-22-3

Alternative names

16α, 17α-22 R, S-propylmethylenedioxypregna-1, 4-diene-1β, 21-diol-3, 20-dione

Applicant

Private applicant

Current scheduling

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

Schedule 4

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

Schedule 2

BUDESONIDE in aqueous nasal sprays delivering 64 micrograms or less of budesonide 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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BUDESONIDE

Schedule 4
Schedule 2

Proposed scheduling

Schedule 4 – Amend entry

BUDESONIDE except when included in Schedule 2 or 3.

Schedule 3 - New entry

BUDESONIDE in single ingredient inhalers for the maintenance treatment of asthma in people aged 12 years and older, where the maximum daily dose does not exceed 800 micrograms.

Schedule 2

BUDESONIDE in aqueous nasal sprays delivering 64 micrograms or less of budesonide 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.

Index – Amend entry

BUDESONIDE

Schedule 4
Schedule 3
Schedule 2

Background

Budesonide is a corticosteroid with predominantly glucocorticoid activity. It is used in various dosage forms for a wide variety of conditions such as asthma, chronic obstructive pulmonary disease (COPD) and rhinitis, and is used both locally (via topical administration) and systemically for the treatment of symptoms associated with inflammatory bowel conditions.[13]

The Therapeutic Guidelines recommends the regular use of single low-dose inhaled corticosteroid for patients with symptoms or need for reliever therapy twice per month or more, for the management of asthma in adults and adolescents (known as Step 2 therapy).[14]

The Australian Asthma handbook recommends the regular daily use of single low-dose inhaled corticosteroid treatment for newly diagnosed asthma in adults and adolescents.[15]

Application summary - reasons for proposal

- The benefit of inhaled budesonide as a maintenance treatment for asthma has been well established, including improved clinical outcomes that reduce the risk of morbidity and mortality and a reduction in the number of workdays lost due to illness in patients with well controlled asthma.
- The proposed entry in Schedule 3 of the Poisons Standard would improve access to effective treatment for all those with asthma, especially those living in regional, rural, remote and very remote locations, as they have a higher asthma mortality rate than those in metropolitan areas.
- The pharmacy network is well distributed across Australia. In regional, rural and remote areas that are underserviced by other healthcare professionals, pharmacists are highly trained health care professionals that could provide a greater contribution to the management of asthma for all patients.
- Inhaled budesonide is consistent with the scheduling factors for Schedule 3 substances, as it has a low potential for dependency and risk of misuse, abuse and illicit use, is substantially

[13] MedicinesComplete (Martindale), *Budesonide*: https://www.medicinescomplete.com/#/content/martindale/12463-p?hspl=budesonide
[14] Therapeutic Guidelines for alternative diagnoses to asthma: https://tgldcdp.tg.org.au/viewTopic?topicfile=asthma-introduction-and-diagnosis&sectionId=rsg6-c01-s2#trsg6-c01-tbl2
[15] Australian Asthma Handbook: https://www.asthmahandbook.org.au/resources/medicines-guide/preventers/inhaled-corticosteroids

safe with pharmacist intervention to ensure quality use of medicines, and has a well-defined risk profile although pharmacist intervention is required to monitor safe use.

- The proposed entry in Schedule 3 could, by increasing access to inhaled budesonide, reduce the overuse/patient reliance on short-acting beta2-agonists (SABAs, e.g. salbutamol), which are currently widely used due to the rapid symptom relief they provide. Overuse of SABAs increases the risk of poor patient outcomes such as the likelihood of exacerbations of asthma symptoms and hospitalisation. Providing pharmacists with a more effective treatment option would achieve better health outcomes for patients.
- Studies evaluating the effectiveness of intervention by pharmacists to improve asthma control found significantly improved patient inhaler technique and adherence to preventer medication, and reduction in the use of reliever medication and the frequency of night-time awakenings due to asthma.
- The Therapeutic Guidelines and the Australian Asthma Handbook recommend the use of a stepwise approach to selecting and adjusting medication for the treatment of asthma. Maintenance treatment should be the lowest effective dose of an inhaled corticosteroid to adequately control symptoms and reduce the need for reliever medication.

Key uses / expected use

Medicine

Australian regulations

- Budesonide is listed as an ingredient on the TGA Ingredient Database.[16]
  - 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; and
  - Not available as an equivalent ingredient in any application.
- As of April 2022, there were 45 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[17] that contain budesonide as an active ingredient. These include 30 prescription medicines, 7 non-prescription medicines and 8 export only medicines.
- Budesonide is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[18] No. 3 of 2022.
- The Therapeutic Goods (Medicines Advisory Statements) Specification 2021[19] does not contain any warning statements in regard to budesonide.
- Since January 2012, there are 283 reports of adverse events for products containing budesonide as an active ingredient on the Database of Adverse Event Notifications (DAEN).[20] 138 reports identified budesonide as the single suspected medicine. The reactions reported

[16] TGA Ingredient Database: https://www.ebs.tga.gov.au/
[17] ARTG database: https://www.tga.gov.au/artg
[18] Therapeutic Goods (Permissible Ingredients) Determination No. 3 2022: https://www.legislation.gov.au/Details/F2022L00496
[19] Therapeutic Goods (Medicines Advisory Statements) Specification 2021: https://www.legislation.gov.au/Details/F2019L00213
[20] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx

were diverse in nature and included varied respiratory symptoms, as well as a significant number of reports of ineffectiveness or exacerbation of the condition.

- As of April 2022, there are two products containing budesonide listed on the Public Chemical Registration Information System Search (PubCRIS).[21]
- There were no adverse experiences recorded for budesonide in the APVMA Adverse Experience Reporting Program database (AERP)[22] between 2011-2021.
- The TGA prescribing medicines in pregnancy database[23] classifies budesonide as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
Budesonide	A	Respiratory system	Inhalation agents	Preventative aerosols and inhalations
Budesonide	A	Endocrine system	Corticosteroids	Inhalation/ intranasal
Budesonide	B3	Alimentary system	Antidiarrhoeals	

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 fetus having been observed.

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.

International regulations

- Budesonide is included in the WHO Model List of Essential Medicines 2019 in nasal spray and aerosol for inhalation formulations.[24]
- The Health Products Regulatory Authority of Ireland[25] regulates budesonide as a prescription only medicine.

[21] Public Chemical Registration Information System Search (PubCRIS): https://portal.apvma.gov.au/pubcris
[22] APVMA Adverse Experience Reporting Program: database (AERP) https://apvma.gov.au/node/10946
[23] TGA prescribing medicines in pregnancy database: https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[24] WHO Model List of Essential Medicines 2019: https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06
[25] Health Products Regulatory Authority of Ireland: https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/

- The United States Food and Drug Administration[26] regulates budesonide in inhalational suspensions and for systemic use as a prescription only medicine. Budesonide when used in nasal sprays is available as an over-the-counter (non-prescription) medicine.
- The Canadian (Health Canada) Drug Product Database[27] restricts all forms of budesonide to prescription only.
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe),[28] budesonide is available as both a prescription only and a Pharmacy Only medicine, the latter when used "for the treatment or prophylaxis of allergic rhinitis in adults and children over 12 years of age in aqueous nasal sprays delivering up to 64 micrograms per actuation and when the maximum recommended daily dose is no greater than 400 micrograms (200 micrograms per nostril)".

2.3 N,α-Dimethyl-3,4-(methylenedioxy)phenylethylamine (MDMA)

Proposal

The applicant has proposed creation of a Schedule 8 entry for the use of MDMA as part of psychotherapy for treatment resistant mental illness in medically controlled environments in certain circumstances. MDMA is currently listed in Schedule 9, which limits use to authorised research and analytical purposes only.

CAS number

42542-10-9 (as base)

Alternative names

1-(1,3-benzodioxol-5-yl)-N-methylpropan-2-amine; methylenedioxymethamphetamine; midomafetamine; α -dimethyl-3,4-(methylenedioxy)phenylethylamine; 3,4-methylenedioxy-N,alpha-dimethylphenylethylamine

Applicant

Private applicant

Current scheduling

MDMA is currently included in Schedule 9 of the Poisons Standard as follows:

Schedule 9

N, α -DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE *(MDMA).

[26] United States Food and Drug Administration: https://www.accessdata.fda.gov/scripts/cder/daf/
[27] Canadian (Health Canada) Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[28] New Zealand Medicines and Medical Devices Safety Authority (Medsafe): https://www.medsafe.govt.nz/profs/class/classintro.asp

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N,α-DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE
cross reference: 3,4-METHYLENEDIOXY-N-α-DIMETHYLPHENYLETHYLAMINE, MDMA

Schedule 9

Proposed scheduling

Schedule 9 – Amend entry

N,α-DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE (MDMA) **except** when separately specified in Schedule 8.

Schedule 8 – New entry

N,α-DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE (MDMA) for use in the treatment of treatment resistant mental illness when:

a) used as part of psychotherapy in medically controlled environments; and
b) under the authorisation of a treating psychiatrist who has received specific training in the use of this substance as part of therapy; and
c) where the patient's diagnosis and the proposed treatment plan has been confirmed by at least two independent reviewing psychiatrists; and
d) where the substance has been manufactured in accordance with the *Narcotic Drugs Act 1967*; and/or
e) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the *Therapeutic Goods Act 1989*; and/or
f) in therapeutic goods supplied in accordance with the *Therapeutic Goods Act 1989*.

Appendix D – New entry

Additional controls on possession or supply of poisons included in Schedule 4 or 8	
Item 3	Poisons available only from or on the prescription or order of a medical practitioner authorised or approved by the Secretary of the Commonwealth Department of Health and Ageing under section 19 of the *Therapeutic Goods Act 1989*
	N,α-DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE *(MDMA).
Item 5	Poisons for which possession without authority is illegal (e.g. possession other than in accordance with a legal prescription)
	N,α-DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE *(MDMA).

Appendix F – New entry

N,α -DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE *(MDMA).

Warning Statement: 36 (For use under medical supervision only)

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N,α-DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE (MDMA)

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Appendix F, Part 3

Background

This proposal is from the same applicant whose application in relation to MDMA was considered at the November 2020 meeting of the Advisory Committee on Medicines Scheduling (ACMS). The ACMS consideration was followed by an Independent Expert Report on the state of evidence into the therapeutic value of MDMA in the treatment of mental illness. The Delegate made a final decision not to amend the Poisons Standard in relation to MDMA on 15 December 2021 (the **previous MDMA decision**).

Prior to the Final Decision on MDMA,

Application summary - reasons for proposal

- In the present application, the applicant seeks to address some of the key issues raised in the previous MDMA decision, including the risk of diversion and the lack of established therapeutic value for this substance, through provision of additional evidence of therapeutic benefit.
- The application asserts that the benefits of the use of MDMA in the manner specified outweigh the risks of diversion and/or translation as they would exist under the proposed scheduling. This is due in part to the serious medical conditions that the substance is proposed to treat and therefore the significance of the therapeutic benefit that may be derived from use of the substance in a clinical setting.
- The applicant states that the risk of diversion is mitigated by the controls placed on Schedule 8 medicines, with comparison to other substances of concern, e.g. ketamine, cocaine, and several opioids which are included in Schedule 8. Medical grade, high purity MDMA is also much more expensive than the substance typically used in recreational setting, which suggests that diversion by unscrupulous pharmacists and doctors is unlikely.
- In addressing the issue of the established therapeutic value of MDMA, the applicant states that further evidence for the use of this substance in the treatment of mental health conditions, including PTSD, has emerged since the previous MDMA decision. In particular, the applicant cites a phase 3 study published in June 2021.[29]
- In comparison to the previous application, this present application proposes several additional conditions and controls on Schedule 8 products containing MDMA. In particular, the need for adequate expertise, procedures and standards are addressed by protocols established in recent clinical trials and an existing certified training course available for health professionals in the administration of these substances to patients and applications of associated therapies.
- While recognising that MDMA is included in Schedule I of the *United Nations Convention on Psychotropic Substances 1971*, the applicant indicates that Article 7 of that document

[29] Mitchell *et al*, Nature Medicine Journal, Vol 27, June 2021, pp 1025-33.

provides legal provision to access the substance for "very limited medical purposes by duly authorized persons, in medical or scientific establishments which are directly under the control of…Governments or specifically approved by them". By inclusion of the additional controls and conditions in this proposal, the applicant claims that this condition is met and should not inhibit the rescheduling of MDMA on the limited basis in the application.

- The applicant states that MDMA does not fit within the requirements of a Schedule 9 substance and more closely reflects the requirements of Schedule 8 in certain circumstances. These include demonstrated therapeutic benefits for individuals suffering from post-traumatic stress disorder (PTSD) whose condition has not improved after standard forms of treatment, and high remission rates shown in clinical trials when used in a medically controlled environment. Additionally, Schedule 8 controls will provide access for at-risk patients who may not qualify for treatment via clinical trial.
- The current Schedule 9 classification of MDMA poses a barrier to research (cost, stigma and difficulty accessing the substance) and its evidence-based use in a medically controlled environment. Reclassifying MDMA as a Schedule 8 substance may reduce cost and improve ease of access for researchers, medical practitioners and patients with conditions that are resistant to existing treatments.
- Medicinal MDMA is well-tolerated and does not produce dependence, as defined in the Diagnostic and Statistical Manual of Mental Disorders or the International Statistical Classification of Diseases. In controlled settings there have been no major adverse events, and minor side effects related to MDMA typically resolve within a few days.
- MDMA-assisted therapy has been granted 'Breakthrough Therapy' status by the US Food and Drug Administration (FDA), expediting its consideration for approval as a prescription medicine. The applicant asserts that this designation highlights the FDA's anticipation that MDMA-assisted therapies may offer substantial advantage over current treatments.
- The FDA has approved an "Expanded Access" scheme using MDMA for PTSD in patients who have limited treatment options. Israel launched a Compassionate Use program for MDMA-assisted therapy for PTSD in 2019, and Switzerland also has a compassionate use program for MDMA with individual authorisations by the Federal Office of Public Health. Recently, the Australian Therapeutic Goods Administration (TGA) approved the use of MDMA-assisted therapy for the treatment of a patient with treatment resistant PTSD under the Special Access Scheme.[30]
- According to the guidelines of Schedule 8 controlled substances in the Poisons Standards, MDMA used for this purpose would adhere to strict safety protocols for supply through health care providers in a medically controlled environment.

Key uses / expected use

Medicine

[30] See also 'Australian Regulations' section for more information about Special Access Scheme approvals.

Australian regulations

- MDMA is not listed as an ingredient on the TGA Ingredient Database.[31]
- As of April 2022, there were no medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[32] that contain MDMA as an active ingredient.
- MDMA is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[33] No.3 of 2022.
- There are no warning statements pertaining to MDMA in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.[34]
- As of April 2022, there were no reports of adverse events for products containing MDMA as an active ingredient on the Database of Adverse Event Notifications (DAEN).[35]
- As of April 2022, there were no products containing MDMA listed on the Public Chemical Registration Information System Search (PubCRIS).[36]
- The TGA prescribing medicines in pregnancy database[37] does not contain an entry for MDMA.
- The TGA's current policy regarding access to MDMA via Special Access Scheme (SAS) Category B is that evidence of state or territory approval is required prior to TGA approval. Past TGA approvals for a small number of SAS Category B applications were predicated on the applicant ensuring themselves that access via this scheme complied with state and territory requirements and legislation, including the Poisons Standard, and did not result in patient access.

International regulations

- MDMA is listed as a Schedule I drug under the United Nations 1971 Convention on Psychotropic Substances.[38]
- MDMA is listed as a Schedule I (controlled substance) drug under the United States (US) Psychotropic Substances Act.[39]
- MDMA is listed as a controlled drug under the United Kingdom (UK) Misuse of Drugs Act 1971.[40]

[31] TGA Ingredient Database: https://www.ebs.tga.gov.au/
[32] ARTG database: https://www.tga.gov.au/artg
[33] Therapeutic Goods (Permissible Ingredients) Determination No. 3 2022: https://www.legislation.gov.au/Details/F2022L00496
[34] Therapeutic Goods (Medicines Advisory Statements) Specification 2021: https://www.legislation.gov.au/Details/F2019L00213
[35] Database of Adverse Event Notifications (DAEN): https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[36] Public Chemical Registration Information System Search (PubCRIS): https://portal.apvma.gov.au/pubcris
[37] TGA prescribing medicines in pregnancy database: https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[38] International drug control conventions – Schedules of the Convention of psychotropic substances of 1972, as at 3 November 2020: https://undocs.org/ST/CND/1/Add.2/Rev.6
[39] US controlled substances orange book (Aug 2020): https://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf
[40] UK *Misuse of drugs Act 1971*: https://www.legislation.gov.uk/ukpga/1971/38/schedule/2

- MDMA is listed as a Schedule III (controlled substance) drug under the Canadian Controlled Drugs and Substances Act.[41]
- According to the New Zealand Medicines and Medical Devices Safety Authority (MedSafe)[42], in New Zealand, MDMA is classified as a class B1 controlled drug (i.e. a drug that poses a high risk of harm if misused) and there are restrictions on prescribing.

2.4 Psilocybine

Proposal

The applicant has proposed the creation of a Schedule 8 entry for the use of psilocybine in combination with psychotherapy for treatment-resistant mental illness in medically controlled environments in certain circumstances. Psilocybine is currently included in Schedule 9, which limits use to authorised research and analytical purposes only.

CAS Number

520-52-5

Alternative names

[3-(2-dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate; psilocybin

Applicant

Private applicant

Current scheduling

Psilocybine is currently included in Schedule 9 of the Poisons Standard as follows:

Schedule 9

PSILOCYBINE

Index

PSILOCYBINE

Schedule 9

Proposed scheduling

Schedule 9 – Amend entry

PSILOCYBINE **except** when separately specified in Schedule 8

[41] Canadian Controlled Drugs and Substances Act: https://laws-lois.justice.gc.ca/eng/acts/C-38.8/section-sched95602.html?txthl=psilocybin

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

Schedule 8 – New entry

PSILOCYBINE for use in the treatment of treatment resistant mental illness when:

a) used as part of psychotherapy in medically controlled environments; and
b) under the authorisation of a treating psychiatrist who has received specific training in the use of this substance as part of therapy; and
c) where the patient's diagnosis and the proposed treatment plan has been confirmed by at least two independent reviewing psychiatrists; and
d) where the substance has been manufactured in accordance with the *Narcotic Drugs Act 1967*; and/or
e) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the *Therapeutic Goods Act 1989*; and/or
f) in therapeutic goods supplied in accordance with the *Therapeutic Goods Act 1989*.

Appendix D – New entry

Additional controls on possession or supply of poisons included in Schedule 4 or 8	
Item 3	Poisons available only from or on the prescription or order of a medical practitioner authorised or approved by the Secretary of the Commonwealth Department of Health and Ageing under section 19 of the *Therapeutic Goods Act 1989*
	PSILOCYBINE.
Item 5	Poisons for which possession without authority is illegal (e.g. possession other than in accordance with a legal prescription)
	PSILOCYBINE.

Appendix F – New entry

PSILOCYBINE.

Warning Statement: **36** (For use under medical supervision only)

Index – Amend Entry

PSILOCYBINE

Schedule 9
Schedule 8
Appendix D, Item 3
Appendix D, Item 5
Appendix F, Part 1

Background

This proposal is from the same applicant whose application in relation to psilocybine was considered at the November 2020 meeting of the Advisory Committee on Medicines Scheduling (ACMS). The ACMS consideration was followed by an Independent Expert Report on the state of

evidence for the therapeutic value of psilocybine in the treatment of mental illness. The Delegate made a final decision not to amend the Poisons Standard in relation to psilocybin on 15 December 2021 (the **previous psilocybine decision**).

Psilocybine is the phosphorylated analogue of psilocine. Both compounds are present in most psychedelic mushrooms.

Application summary - reasons for proposal

- In the present application, the applicant seeks to address some of the key issues raised in the previous psilocybine decision.
- The application asserts that the benefits of the use of psilocybine in the manner specified outweigh the risks of diversion and/or translation as they would exist under the proposed scheduling. This is due in part to the serious medical conditions that the substance is proposed to treat and therefore the significance of the therapeutic benefit that may be derived from use of the substance in a clinical setting.
- The applicant states that the proposed entry in Schedule 8 will make it easier for Australians suffering from depression, anxiety disorders and/or substance abuse (and potentially other illnesses such as anorexia nervosa and obsessive-compulsive disorder) to access psilocybine-assisted therapy through their psychiatrists and specialist addiction physicians (with supporting therapists) in strictly medically controlled environments. It will also reduce impediments, including costs, to clinical research into psilocybine-assisted treatment.
- In addressing the issue of the established therapeutic value of psilocybine, the applicant states that further evidence for the use of this substance in the treatment of mental health conditions, including treatment resistant depression, has emerged since the previous psilocybine decision. In particular, the applicant cites two separate phase 2 studies published in May 2021[43] and November 2021.[44]
- Psilocybine-assisted therapy can lead to remission in 60-80% of cases of anxiety and depression, whereas current existing treatments lead to remission in a maximum of 35-42% of cases (Griffiths et al., 2016; Ross, 2016; Carhart-Harris, 2016).
- The applicant states that the risk of diversion, as identified in the previous decision, is mitigated by the controls placed on Schedule 8 medicines. This includes comparison to other substances of concern, e.g. ketamine, cocaine, and several opioids which are included in Schedule 8.
- In comparison to the previous application, this present application proposes several additional conditions and controls on Schedule 8 products containing psilocybine. In particular, the need for adequate expertise, procedures and standards are addressed by protocols established in recent clinical trials and an existing certified training course available for health professionals in the administration of these substances to patients and applications of associated therapies.
- While recognising that psilocybine is included in Schedule I of the *United Nations Convention on Psychotropic Substances 1971*, the applicant indicates that Article 7 of that document provides legal provision to access the substance for "very limited medical purposes by duly

[43] Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, et al. Trial of Psilocybin versus Escitalopram for Depression. New England Journal of Medicine. 2021;384:1402-11.
[44] COMPASS Pathways announces positive topline results from groundbreaking phase IIb trial of investigational COMP360 psilocybin therapy for treatment-resistant depression: https://ir.compasspathways.com/node/7516/pdf

authorized persons, in medical or scientific establishments which are directly under the control of…Governments or specifically approved by them". By inclusion of the additional controls and conditions in this proposal, the applicant claims that this condition is met and should not inhibit the rescheduling of psilocybine on the limited basis in the application.

- In a medically controlled environment psilocybine-assisted therapy is safe, non-addictive, and there is no increase in risk for mental ill-health.
- Two Breakthrough Therapy Designations have been granted for psilocybine by the Food and Drug Administration (FDA) in the United States. The first was to Compass Pathways Limited in 2018 for psilocybine as part of therapy for treatment resistant depression. The second was in 2019 to Usona Institute for psilocybine as part of therapy in the treatment of major depressive disorder. This designation from the FDA acknowledges both the unmet medical need in these broad populations and the potential to offer significant improvements over existing therapies.

Key uses / expected use

Medicine

Australian regulations

- Psilocybine is not listed as an ingredient on the TGA Ingredient Database.[45]
- As of April 2022, there were no medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[46] that contain psilocybine as an active ingredient.
- Psilocybine is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[47] No. 3 of 2022.
- There are no warning statements pertaining to psilocybine in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.[48]
- As of April 2022, there were no reports of adverse events for products containing psilocybine as an active ingredient on the Database of Adverse Event Notifications (DAEN).[49]
- As of April 2022, there were no products containing psilocybine listed on the Public Chemical Registration Information System Search (PubCRIS).[50]
- The TGA's current policy regarding access to psilocybin via Special Access Scheme (SAS) Category B is that evidence of state or territory approval is required prior to TGA approval. Past TGA approvals for a small number of SAS Category B applications were predicated on the applicant ensuring themselves that access via this scheme complied with state and territory requirements and legislation, including the Poisons Standard, and did not result in patient access.

[45] TGA Ingredient Database: https://www.ebs.tga.gov.au/
[46] ARTG database: https://www.tga.gov.au/artg
[47] Therapeutic Goods (Permissible Ingredients) Determination: https://www.legislation.gov.au/Details/F2022L00496
[48] Therapeutic Goods (Medicines Advisory Statements) Specification 2021: https://www.legislation.gov.au/Series/F2021L01888
[49] Database of Adverse Event Notifications (DAEN): https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[50] Public Chemical Registration Information System Search (PubCRIS): https://portal.apvma.gov.au/pubcris

International regulations

- Psilocybine is listed as a Schedule I drug under the United Nations 1971 Convention on Psychotropic Substances.[51]
- Psilocybine is listed as a Schedule I (controlled substance) drug under the United States (US) Psychotropic Substances Act.[52]
- Psilocine is listed as a controlled drug under the *United Kingdom (UK) Misuse of Drugs Act 1971*.[53]
- Psilocybine is listed as a Schedule III (controlled substance) drug under the Canadian Controlled Drugs and Substances Act.[54]
- According to the New Zealand Medicines and Medical Devices Safety Authority (MedSafe)[55] psilocybine is classified in New Zealand as a Class A controlled drug (i.e. is a drug that poses a very high risk of harm when misused) and there are restrictions on its supply, prescribing or administration[56].

2.5 Apronal (allylisopropylacetylurea)

Proposal

This application was initiated by the Delegate in order to clarify the appropriate scheduling for apronal and allylisopropylacetylurea, which are currently in Schedule 4 and Schedule 10 of the Poisons Standard respectively. These entries represent the same substance.

CAS Number

528-92-7

Alternative names

N-carbamoyl-2-propan-2-ylpent-4-enamide; apronalide

Current scheduling

Apronal is currently listed in Schedule 4 of the Poisons Standard as follows:

Schedule 4

APRONAL

[51] The International *Drug Control Conventions – Schedules of the Convention on Psychotropic Substances of 1971*, as at 3 November 2020: https://undocs.org/ST/CND/1/Add.2/Rev.6

[52] Drug Enforcement Agency Controlled substances: https://www.deadiversion.usdoj.gov/schedules/orangebook/c_cs_alpha.pdf

[53] UK *Misuse of Drugs Act 1971*: https://www.legislation.gov.uk/ukpga/1971/38/schedule/2

[54] Canadian Controlled Drugs and Substances Act: https://laws-lois.justice.gc.ca/eng/acts/C-38.8/section-sched95602.html?txthl=psilocybin

[55] NZ MedSafe Classification Database: https://www.medsafe.govt.nz/profs/class/classintro.asp

[56] NZ *Misuse of Drugs Act 1975*: http://www.legislation.govt.nz/act/public/1975/0116/latest/DLM436190.html

Index

APRONAL

Schedule 4

Allylisopropylacetylurea is currently listed in Schedule 10 of the Poisons Standard as follows:

Schedule 10

ALLYLISOPROPYLACETYLUREA for therapeutic use.

Index

ALLYLISOPROPYLACETYLUREA

Schedule 10

Proposed scheduling

Schedule 4 – Delete entry

~~APRONAL~~

Index – Delete entry

~~**APRONAL**~~

~~**Schedule 4**~~

Schedule 10 – Amend entry

APRONAL ~~ALLYLISOPROPYLACETYLUREA for therapeutic use~~

Index – Amend entry

APRONAL
cross reference: ALLYLISOPROPYLACETYLUREA

Schedule 10

Background and reasons for proposal

Apronal/allylisopropylacetylurea is an acylurea-class compound, and due to a similar molecular structure to barbiturates, has activity as a hypnotic.

'Allylisopropylacetylurea' was included in Schedule 4 in January 1955. It was moved to Schedule 9 in 1965 and added to Appendix C (now Schedule 10) in 1988. A separate entry for 'apronal' was included in Schedule 4 of the Poisons Standard in 1998.

The propensity for apronal/allylisopropylacetylurea to cause thrombocytopenic purpura is long established, having been first reported in 1933 and appearing in peer reviewed journals throughout the 1950s.[57,58] The haemolytic reactions produced by apronal (brand name *Sedormid*) were one of the first examples of drug-dependent antibody interaction to be fully

[57] Grant, K *Diagnosis of Sedormid purpura*, British Medical Journal, 1953 Jul 18;2(4828):128-31: https://www.bmj.com/content/2/4828/128

[58] Kallos, P *Sedormid Purpura: An immunological study of a form of drug hypersensitivity*, Chemical Immunology and Allergy, *1952, vol 3, pp 531-576*

characterised, informing knowledge about the underlying immunological mechanisms. Apronal may also induce cytochrome P-450 enzymatic activity, leading to drug-drug interactions.

As apronal and allylisopropylacetylurea are widely accepted to be synonyms for the same substance, these entries in the Poisons Standard should be unified. No products containing apronal or allylisopropylacetylurea are currently marketed in Australia.

Key uses / expected use

Medicine

Australian regulations

- Neither apronal nor allylisopropylacetylurea appear in the TGA Ingredient Database.[59]
- As of April 2022, there are no medicines active on the Australian Register of Therapeutic Goods (ARTG)[60] that contain apronal or allylisopropylacetylurea as an active ingredient.
- Neither apronal nor allylisopropylacetylurea appear in the Therapeutic Goods (Permissible Ingredients) Determination[61] No. 3 of 2022.
- Neither apronal nor allylisopropylacetylurea appear in the TGA prescribing medicines in pregnancy database.[62]
- There are no warning statements pertaining to apronal or allylisopropylacetylurea in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019.[63]
- The Database of Adverse Event Notifications (DAEN)[64] does not contain data for apronal or allylisopropylacetylurea.
- As of April 2022, there were no products containing apronal or allylisopropylacetylurea listed on the Public Chemical Registration Information System Search (PubCRIS).[65]

International regulations

- The Canadian (Health Canada) Drug Product Database[66] does not contain an entry for apronal or allylisopropylacetylurea.
- The United States Food and Drug Administration Approved Drug Products Database (Drugs@FDA)[67] does not contain an entry for apronal or allylisopropylacetylurea.

[59] TGA Ingredient Database: https://www.ebs.tga.gov.au/
[60] ARTG database: https://www.tga.gov.au/artg
[61] Therapeutic Goods (Permissible Ingredients) Determination: https://www.legislation.gov.au/Details/F2022L00496
[62] TGA prescribing medicines in pregnancy database: https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[63] Therapeutic Goods (Medicines Advisory Statements) Specification 2019: https://www.legislation.gov.au/Details/F2019L00213
[64] Database of Adverse Event Notifications (DAEN): https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[65] Public Chemical Registration Information System Search (PubCRIS): https://portal.apvma.gov.au/pubcris
[66] Canadian (Health Canada) Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[67] FDA Approved Drug Products Database: https://www.accessdata.fda.gov/scripts/cder/daf/

- The New Zealand Medicines and Medical Devices Safety Authority (MedSafe)[68] lists apronal as a prescription medicine.
- The European Commission general index[69] does not contain an entry for apronal or allylisopropylacetylurea.
- Apronalide is approved for use in Japan, where it is combined with paracetamol and caffeine as an OTC analgesic medicine.

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

[69] European Commission https://ec.europa.eu/health/documents/community-register/html/reg_index_inn.htm

3. Proposed amendments referred for scheduling advice to the Joint ACMS-ACCS #31, June 2022

3.1 Helional

Proposal

The applicant has proposed the creation of new Schedule 6 and Schedule 10 entries for the substance helional, which is not currently scheduled. Helional is used as a fragrance and flavouring agent, but may be used in the manufacture of illicit substances, and may also be toxic by ingestion. The proposal is to prohibit internal use of helional except in low concentrations in therapeutic and food preparations, and place labelling and storage requirements on helional in most other preparations for external use.

CAS Number

1205-17-0

Alternative names

3-(1,3-benzodioxol-5-yl)-2-methylpropanal; 2-methyl-3-(3,4-methylenedioxyphenyl)propanal; 2-piperonylpropanal

Applicant

Private applicant

Current scheduling

Helional is not specifically scheduled in the current Poisons Standard.

Proposed scheduling

Schedule 10 – New entry

HELIONAL for internal use except:

a) in therapeutic preparations containing 5 per cent or less of helional; or

b) as a food additive in food preparations containing 5 per cent or less of helional.

Schedule 6 – New entry

HELIONAL except:

a) for internal use; or

b) in other preparations containing 10 per cent or less of helional.

Appendix E, Part 2 - FIRST AID INSTRUCTIONS FOR POISONS – New entry

HELIONAL

Standard Statements

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.);
G1 (Urgent hospital treatment is likely to be needed.);
G3 (If swallowed, do NOT induce vomiting.);
E1 (If in eyes wash out immediately with water.); and
S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.)

Appendix F, Part 3 - WARNING STATEMENTS AND GENERAL SAFETY DIRECTIONS FOR POISONS – New entry

HELIONAL

a) In preparations for therapeutic use: Safety Direction **1** (Avoid contact with eyes)

b) Other than for therapeutic use: Safety Directions **1** (Avoid contact with eyes) and **4** (Avoid contact with skin).

Index – New entry

HELIONAL

cross-reference: 2-PIPERONYLPROPANAL, 3-(3,4-METHYLENEDIOXYPHENYL)-2-METHYLPROPANAL, OCEAN PROPANAL

Schedule 10
Schedule 6
Appendix E, Part 2
Appendix F, Part 3

Background

- Helional is an aldehyde derivative of heliotropin. At low concentrations, helional is used as a flavouring and fragrance additive in therapeutic goods, as a flavouring agent in food, and in cosmetics, perfumery, deodorants, odorants, and cleaning products as a fragrance.
- There is increasing concern from law enforcement groups that helional is being used as a precursor to manufacture illicit substances, such as 3,4-methylenedioxyamphetamine (MDA), in clandestine laboratories.

Application summary - reasons for proposal

- According to Australian Government sources, helional has been identified as a substance used as a precursor in the illicit production of MDA and other amphetamine-type stimulants.[70]
- Helional is commercially synthesised from piperonyl (heliotropin) and detailed information about the steps in production of MDA from helional is publicly available.

[70] *Final report of the National ICE Taskforce*, Australian Government: https://www.pmc.gov.au/sites/default/files/publications/national_ice_taskforce_final_report.pdf

- Australian states and territories have taken steps towards regulating the availability of helional due to its illicit use, including restricting the use of helional and/or helional related substances in Victoria[71] and NSW[72] as recognised precursors to illicit substances.
- International agencies have also identified helional use in clandestine drug synthesis.[73]

Key uses / expected use

Food additive (flavouring), industrial use.

Australian regulations

- According to the TGA Ingredient Database[74] 2-methyl-3-(3,4-methylenedioxyphenyl)propanal (aka helional) is:
  - Not available for use as an active ingredient in any therapeutic good,
  - Available for use as an excipient ingredient in devices, listed medicines, and over-the-counter medicines, with the following restrictions:

Restriction	Applies to
Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance.	Listed medicines
If used in a flavour the total flavour concentration in a medicine must be no more than 5%.	Listed medicines
If used in a fragrance the total fragrance concentration in a medicine must be no more 1%	Listed medicines

  - Not available as an equivalent ingredient in any application.
- As of April 2022 there were no medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[75] that contain helional as an active ingredient. There are 88 products that contain helional (as 2-methyl-3-(3,4-methylenedioxyphenyl)propanal) as an excipient, including sunscreens, disinfectants, topical gels, and shampoos.

[71] Drugs, Poisons and Controlled Substances (Precursor Chemicals) Regulations 2017 (VIC): https://engage.vic.gov.au/download/document/17811
[72] Drug Misuse and Trafficking Regulation 2021 (NSW): http://classic.austlii.edu.au/au/legis/nsw/consol_reg/dmatr2021347/
[73] EMCDQA: Drug precursor developments in the European Union (europa.eu)
[74] TGA Ingredient Database: https://www.ebs.tga.gov.au/
[75] ARTG database: https://www.tga.gov.au/artg

- According to the Therapeutic Goods (Permissible Ingredients) Determination[76] No. 3 of 2022, 2-methyl-3-(3,4-methylenedioxyphenyl)propanal is permitted to be included in listed medicines as follows:

Item	Ingredient name	Purpose	Specific requirements
144	2-METHYL-3-(3,4-METHYLENEDIOXYPHENYL)PROPANAL	E	Permitted for use only in combination with other permitted ingredients as a flavour or a fragrance. If used in a flavour the total flavour concentration in a medicine must be no more than 5%. If used in a fragrance the total fragrance concentration in a medicine must be no more 1%.
E = excipient for a medicine meaning an ingredient that is not an active ingredient or a homoeopathic preparation ingredient			

- Helional is not included in the TGA prescribing medicines in pregnancy database.[77]
- Helional is not included in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.[78]
- As of April 2022 there were no reports of adverse events for products containing helional as an active ingredient on the Database of Adverse Event Notifications (DAEN).[79]
- As of April 2022 there were no products containing helional listed on the Public Chemical Registration Information System Search (PubCRIS).[80]

International regulations

- The United States Food and Drug Administration considers 3-(3,4-methylenedioxyphenyl)-2-methylpropanal a "substance added to food", with no restrictions or prohibitions.[81]
- The United States Flavor and Extract Manufacturers Association (FEMA) considers 3-(3,4-methylenedioxyphenyl)-2-methylpropanal as part of the "Generally regarded as safe" entry 4599 for cinnamyl derivatives used as flavour ingredients.[82]

[76] Therapeutic Goods (Permissible Ingredients) Determination: https://www.legislation.gov.au/Details/F2022L00496
[77] TGA prescribing medicines in pregnancy database: https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[78] Therapeutic Goods (Medicines Advisory Statements) Specification 2019: https://www.legislation.gov.au/Details/F2019L00213
[79] Database of Adverse Event Notifications (DAEN): https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[80] Public Chemical Registration Information System Search (PubCRIS): https://portal.apvma.gov.au/pubcris
[81] United States Food and Drug Administration: Substances Added to Food (formerly EAFUS) (fda.gov)
[82] United States Flavor and Extract Manufacturers Association (FEMA), *4599 3-(3,4-METHYLENEDIOXYPHENYL)-2-METHYLPROPANAL*: https://www.femaflavor.org/flavor-library/3-34-methylenedioxyphenyl-2-methylpropanal

- The New Zealand's Inventory of Chemicals has an entry for 1,3-Benzodioxole-5-propanal, α-methyl- without restriction.[83]
- As of April 2022 the Food and Agriculture Organisation of the United Nations have a tentative specification for 3-(3,4-methylenedioxyphenyl)-2-methylpropanal as a flavouring.[84]

3.2 Hydroxypinacolone retinoate

Proposal

The applicant has presented two proposed amendments to the Schedule 4 entry for tretinoin to exclude its salts and derivatives and/or hydroxypinacolone retinoate (HPR) for use in topical preparations containing 0.5 per cent or less of the substance.

CAS Number

893412-73-2

Alternative names

(3,3-dimethyl-2-oxybutyl) (2E,4E,6E,8E)-3,7-dimethyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenoate; Retinoic acid, 1-hydroxy-3,3-dimethyl-2-butanone ester, trans; Granactive retexture T; MDI 101.

Applicant

Private applicant

Current scheduling

HPR is not specifically scheduled in the current Poisons Standard, however is regarded as a derivative of the scheduled substance tretinoin, which is included in the Poisons Standard as follows:

Schedule 4

#TRETINOIN

Appendix D, Item 4

4. Poisons available only from or on the order of a specialist physician and for which the prescriber must, where the patient is a woman of child bearing age:

   a) ensure that the possibility of pregnancy has been excluded prior to commencement of treatment; and

   b) advise the patient to avoid becoming pregnant during or for a period of 1 month after completion of treatment.

[83] New Zealand Environmental Protection Authority: New Zealand Inventory of Chemicals (NZIoC) | EPA

[84] Food and Agriculture Organisation of the United Nations, *Food safety and quality*: https://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-flav/details/en/c/2228/

TRETINOIN for human oral use.

Appendix F, Part 3

Substance	WARNING STATEMENTS
TRETINOIN	
a) for human oral use	7. WARNING – cause 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.
b) for topical use	62. Do not use if pregnant.
	77. WARNING – May cause birth defects.

Appendix L, Part 2

TRETINOIN – similar warning statements as required by the Appendix F entry for this substance (see above)

Index

TRETINOIN

Schedule 4
Appendix D, Item 4
Appendix F, Part 3
Appendix L, Part 2

Proposed scheduling

Proposal A

Schedule 4 – Amend Entry

TRETINOIN **except** the ester hydroxypinacolone retinoate for topical use in cosmetic preparations containing 0.5 per cent or less.

Proposal B

Schedule 4 – Amend Entry

TRETINOIN **except** in preparations containing tretinoin salts or derivatives for topical use containing 0.5 per cent or less.

There are no proposed amendments to the Appendices or Index for this substance.

Background

HPR is a synthetic short chain ester derivative of tretinoin which does not readily hydrolyse into tretinoin. HPR is used in topical cosmetics at low concentrations and marketed for its similarity to retinol (Vitamin A).

This application is in response to scheduling advice that HPR is captured in the Poisons Standard as a derivative of the Schedule 4 substance tretinoin, and seeks exemption from scheduling either for HPR specifically (Proposal A), or for all derivatives of tretinoin in general (Proposal B), at low concentrations for topical use.

Application summary - reasons for proposal

- The claimed benefits of topical products containing HPR are limited to appearances and maintenance of good conditions (reduces the signs of aging, smooths wrinkles, firms/conditions skin) – this meets the definition of a cosmetic and does not require medical supervision or intervention.
- HPR has a very low potential for causing harm as it is non-corrosive, has very low toxicity, and has very low potential to be a health hazard. There is a history of safe usage for HPR and over a decade of cosmetic use has not found a reported incident of irritation.
- There is global harmonisation and support that HPR is safe in concentrations of up to 0.5% for topical cosmetic use and is not likely to present a high risk of dependency, abuse, misuse, or illicit use. This is consistent with Health Canada's consideration that retinol and its equivalents are safe up to 0.5% for use in cosmetics and personal care products.
- A stem cell development toxicity screening test demonstrated that the conversion from HPR to tretinoin is unlikely and developmental toxicity from dermal exposure is unlikely to occur.
- A tape strip test, in which HPR at a concentration of 0.3% was applied to the forearm of volunteers, later tape stripped four times and analysed for tretinoin by HPLC. Tretinoin was not detected at any stripped level, which demonstrates that tretinoin formation through in vivo hydrolysis does not occur at significant levels.
- The risk of poisoning is not higher than topical forms of retinol. Topical use of retinol and tretinoin does not lead to increases in systemic plasma levels of these substances.

Key uses / expected use

Cosmetic use

Australian regulations

- HPR is not included in the TGA Ingredient Database.[85] According to the TGA Ingredient Database, tretinoin is:
  - Available as an active ingredient in biological, export only, 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 April 2022, there were no medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[86] that contain HPR as an active ingredient. Six medicines contain tretinoin as an active ingredient, including five prescription medicines and one export only

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

medicine. Five of the registered tretinoin medicines were for topical use, and one oral dosage form.

- HPR and tretinoin are not permitted to be included in listed medicines as they are not included in the Therapeutic Goods (Permissible Ingredients) Determination[87] No.3 of 2022.
- HPR is not included in the TGA prescribing medicines in pregnancy database. The TGA prescribing medicines in pregnancy database[88] classifies tretinoin as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
clindamycin / tretinoin	D	Drugs used in Dermatology	Topical	
tretinoin	D	Drugs used in Dermatology	Topical	
tretinoin (oral)	X	Antineoplastic agents		

Category D – Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Category X – Drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

- There are no warning statements pertaining to HPR or tretinoin in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.[89]
- Between January 1971 and April 2022, there were no reports of adverse events for products containing HPR as an active ingredient on the Database of Adverse Event Notifications (DAEN).[90]. There were 82 reports of adverse events for products containing tretinoin as an active ingredient on the DAEN including 46 reports where tretinoin was the single suspected medicine and 14 cases where death was a reported outcome. The majority of reports were associated with congenital, familial and genetic disorders, and/or skin and subcutaneous tissue disorders.
- As of April 2022, there were no products containing HPR or tretinoin listed on the Public Chemical Registration Information System Search (PubCRIS).[91]

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

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

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

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

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

International regulations

- HPR is not included in the WHO Model List of Essential Medicines 2019. Tretinoin is included in the WHO Model List of Essential Medicines 2019[92] as all-trans retinoid acid.
- HPR is not listed in the United States Food and Drug Administration Approved Drug Products Database. Tretinoin for both topical and oral use is regulated as a prescription only medicine.
- HPR is listed in the European Commission database for information on cosmetic substances and ingredients[93] but does not carry any conditions. Tretinoin is prohibited in cosmetic products by the European Commission and listed in Annex II of EU Cosmetics Regulations.[94]
- HPR is not listed in the European Commission Register of medicinal products.[95]
- Tretinoin is classified as a prescription medicine by the New Zealand Medicines and Medical Devices Safety Authority (MedSafe).[96] HPR is not listed in this database.
- Tretinoin is listed as a prescription medicine in all formulations by the Canadian (Health Canada) Drug Product Database.[97]
- Tretinoin is listed in Health Canada's Cosmetic Ingredient Hotlist,[98] under the synonym of retinoic acid. In October 2020, Health Canada proposed a revision to the entry to clarify that derivatives and salts of retinoic acid are captured, as they are unsuitable for use in cosmetics due to their inclusion in Health Canada's Prescription Drug List. It was also noted that prescription medicines for topical use containing tretinoin at concentrations as low as 0.01% are listed in Health Canada's Drug Product Database and available scientific evidence suggests that derivatives of retinoic acid display an innate retinoic acid activity, as supported by their therapeutic use in topical products at concentrations that overlap with the therapeutic range of retinoic acid.[99]

[92] WHO Model List of Essential Medicines 2019: https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06
[93] European Commission database for information on cosmetic substances and ingredients database: https://ec.europa.eu/growth/tools-databases/cosing/
[94] Regulation (EC) No 1223/2009: https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32009R1223&from=EN
[95] European Commission: https://ec.europa.eu/health/documents/community-register/html/reg_index_inn.htm
[96] New Zealand Medicines and Medical Devices Safety Authority (MedSafe): https://www.medsafe.govt.nz/profs/class/classintro.asp
[97] Canadian (Health Canada) Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[98] Health Canada List of Ingredients that are Prohibited for Use in Cosmetic Products: https://www.canada.ca/en/health-canada/services/consumer-product-safety/cosmetics/cosmetic-ingredient-hotlist-prohibited-restricted-ingredients/hotlist.html
[99] Health Canada Notice to Stakeholders concerning review of the Cosmetic Ingredient Hotlist:https://www.canada.ca/en/health-canada/services/consumer-product-safety/cosmetics/notice-stakeholders-proposed-updates-cosmetic-ingredient-hotlist.html

3.3 N,α-Dimethyl-3,4-(methylenedioxy)phenylethylamine (MDMA) and 3,4-methylenedioxyamfetamine (MDA)

Proposal

The applicant has proposed amendment of the current Schedule 9 entries for N,α-dimethyl-3,4-(methylenedioxy)phenylethylamine (MDMA) and 3,4-methylendioxyamfetamine (MDA) to reference their respective international non-proprietary names (INNs) midomafetamine and tenamfetamine, with retention of the original names as cross-references in the respective index entries for each substance.

CAS number

MDMA: 42542-10-9

MDA: 4764-17-4

Alternative names

MDMA: 3,4-methylenedioxymethamphetamine; midomafetamine; N,α-dimethyl-3,4-methylenedioxy-phenylethylamine

MDA: 3,4-methylenedioxyamphetamine; tenamfetamine

Applicant

Private applicant

Current scheduling

MDMA is currently included in Schedule 9 of the Poisons Standard as follows:

Schedule 9

N, α -DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE *(MDMA).

Index

N, α -DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE
cross reference: 3,4-METHYLENEDIOXY-N-α-DIMETHYLPHENYLETHYLAMINE, MDMA

Schedule 9

MDA is currently included in Schedule 9 of the Poisons Standard as follows:

Schedule 9

3,4-METHYLENEDIOXYAMFETAMINE *(MDA).

Index

3,4-METHYLENEDIOXYAMFETAMINE *(MDA).
cross reference: 3,4-METHYLENEDIOXYAMPHETAMINE, MDA

Schedule 9

Proposed scheduling

MDMA

Schedule 9 – Amend entry

~~N, α -DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE *(MDMA).~~

MIDOMAFETAMINE.

Index

~~**N, α -DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE *(MDMA).**~~

MIDOMAFETAMINE
cross reference: N,α-DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE 3,4-METHYLENEDIOXY-N-α-DIMETHYLPHENYLETHYLAMINE, MDMA

Schedule 9

MDA

Schedule 9 – Amend entry

~~3,4-METHYLENEDIOXYAMFETAMINE *(MDA).~~

TENAMFETAMINE.

Index

~~**3,4-METHYLENEDIOXYAMFETAMINE *(MDA).**~~

TENAMFETAMINE
cross reference: 3,4-METHYLENEDIOXYAMFETAMINE, 3,4-METHYLENEDIOXYAMPHETAMINE, MDA

Schedule 9

Application summary - reasons for proposal

- While it is noted that N,α-dimethyl-3,4-(methylenedioxy)phenylethylamine is the chemical description used in the United Nations Convention on Psychotropic Substances 1971, INNs are conventionally used throughout the Poisons Standard. For instance, cannabis extracts, psilocybin, amphetamine, methamphetamine, and tetrahydrocannabinoids (THCs) use the INNs or Non-Proprietary Names nabiximols, psilocybine, amfetamine, metamfetamine, and dronabinol, respectively.
- The United Nations Convention on Psychotropic Substances 1971 uses the INN tenamfetamine[100] to refer to MDA.
- The United States Food and Drug Administration (FDA) recognises the INNs midomafetamine for MDMA and tenamfetamine for MDA.[101]

[100] United Nations Convention on Psychotropic Substances (1971): https://www.unodc.org/unodc/en/commissions/CND/conventions.html
[101] United States Global Substance Registration System: https://precision.fda.gov/uniisearch

4. Proposed amendments referred for scheduling advice to ACCS #34, June 2022

4.1 Dichloromethane (methylene chloride)

Proposal

The applicant has proposed the deletion of the existing Schedule 5 entry in the Poisons Standard for dichloromethane, to be replaced by a new entry in Schedule 10. This amendment would effectively prohibit any use of dichloromethane.

CAS Number

75-09-2

Alternative names

Methylene chloride; methylene dichloride; methylene bichloride

Applicant

Private applicant

Current scheduling

Dichloromethane is currently included in Schedule 5 of the Poisons Standard as follows:

Schedule 5

DICHLOROMETHANE (methylene chloride) **except**:

a) in preparations in pressurised spray packs labelled as degreasers, decarbonisers or paint strippers and containing 10 per cent or less of dichloromethane;

b) in other preparations in pressurised spray packs;

c) in paints and tinters containing 5 per cent or less of dichloromethane.

Index

DICHLOROMETHANE
cross reference: METHYLENE CHLORIDE

Schedule 5
Appendix E, Part 2
Appendix F, Part 3

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

Appendix E, Part 2

Standard code	Standard statements
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).
G3	If swallowed, do NOT induce vomiting.
G5	Avoid giving milk or oils.
E1	If in eyes wash out immediately with water.
R1	If inhaled, remove from contaminated area. Apply artificial respiration if not breathing.
S1	If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.
In pressurised spray packs	
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).
G6	If sprayed in mouth, rinse mouth with water.
S1	If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water.

Appendix F, Part 3

Warning statements	Safety directions
a) in paint or lacquer removers	
12: Vapour is harmful to health on prolonged exposure	1: Avoid contact with eyes
16: Forms dangerous gas near radiators or naked flames	4: Avoid contact with skin
	8: Avoid breathing dust (or) vapour (or) spray mist
	11: No smoking

b) other than in paint or lacquer removers	
	1: Avoid contact with eyes
	4: Avoid contact with skin
	8: Avoid breathing dust (or) vapour (or) spray mist
	25: Avoid contact with food

Proposed scheduling

Schedule 10 – New Entry

DICHLOROMETHANE (methylene chloride)

Schedule 5 – Delete Entry

~~DICHLOROMETHANE (methylene chloride) **except**:~~

~~a) in preparations in pressurised spray packs labelled as degreasers, decarbonisers or paint strippers and containing 10 per cent or less of dichloromethane;~~

~~b) in other preparations in pressurised spray packs; or~~

~~c) in paints and tinters containing 5 per cent or less of dichloromethane.~~

Index – Amend Entry

DICHLOROMETHANE
cross reference: METHYLENE CHLORIDE

Schedule 10
~~Schedule 5~~
~~Appendix E, Part 2~~
~~Appendix F, Part 3~~

Appendix E – Delete Entry

~~DICHLOROMETHANE (methylene chloride)~~

~~Standard statements: A, G3, G5, E1, R1, S1~~

~~(in pressurised spray packs): A, G6, S1~~

Appendix F – Delete Entry

~~DICHLOROMETHANE (methylene chloride)~~

~~a) in paint or lacquer removers~~

~~warning statements: 12, 16~~

~~safety directions: 1, 4, 8, 11~~

~~b) other than in pant or lacquer removers~~

~~warning statements: N/A~~

~~safety directions: 1, 4, 8, 25~~

Part 2, Section Seven (Appendix I) – Delete Entry

The Second Group

Substance	Proportion
~~DICHLOROMETHANE (methylene chloride)~~	~~more than 5 per cent by wt~~

Application summary - reasons for proposal

- Methylene chloride is a halogenated hydrocarbon that is commonly utilised for its solvent properties in many consumer products, including paint strippers, degreasers and decarbonisers.
- Due to its volatility, dichloromethane presents an asphyxiation risk for users in poorly ventilated areas. A number of injuries and deaths have been recorded in domestic settings in the USA and Europe related to inhalation of dichloromethane vapours.
- The US Environmental Protection Agency banned use of dichloromethane in domestic paint removal products in 2019 in response to deaths associated with the presence of the substance in these products. Several alternatives to dichloromethane in paints strippers are available, including less toxic chemicals and physical means of paint stripping.

Key uses / expected use

Industrial use, medicines (as an excipient), cosmetics, domestic products as a solvent

Australian regulations

- According to the TGA Ingredient Database,[102] dichloromethane is:
  - Available for use as an active ingredient in biologicals and prescription medicines;
  - Available for use an excipient ingredient in biologicals, devices, export only medicines, listed medicines, over the counter medicines and prescription medicines;
  - Not available as an equivalent ingredient in any application.
- As of April 2022, there were no medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[103] that contain dichloromethane as an active ingredient. Dichloromethane is listed as an excipient in 54 prescription medicines, 8 non-prescription medicines, one export only medicine and one medical device.

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

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

- According to the Therapeutic Goods (Permissible Ingredients) Determination[104] No.3 of 2022, dichloromethane is permitted to be included in listed medicines as follows:

Item	Ingredient name	Purpose	Specific requirements
1797	DICHLOROMETHANE	E	The concentration in the medicine must be no more than 0.06%. The residual solvent limit for Dichloromethane is 6 mg per recommended daily dose.
E = excipient for a medicine meaning an ingredient that is not an active ingredient or a homoeopathic preparation ingredient			

- Dichloromethane is not included in the TGA prescribing medicines in pregnancy database.[105]
- There are no warning statements pertaining to dichloromethane in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.[106]
- As of April 2022, there were no reports of adverse events for products containing dichloromethane as an active ingredient on the Database of Adverse Event Notifications (DAEN).[107]
- As of April 2022, there were no products containing dichloromethane as an active ingredient, constituent or scheduled substance listed on the Public Chemical Registration Information System Search (PubCRIS).[108]
- Safe Work Australia[109] recommend a workplace exposure standard of 50ppm (174 mg/m^3, time-weighted average) of dichloromethane to protect for elevated carboxyhaemoglobin (COHb) and central nervous system (CNS) effects in exposed workers (see Attachment D). Similar workplace limits are imposed in France, Switzerland, Spain and some parts of Canada.

International regulations

- According to the European Chemicals Agency (ECHA), dichloromethane is a suspected carcinogen and under assessment as an endocrine disruptor. The substance has also been identified as a serious eye irritant, a skin irritant and may cause drowsiness or dizziness.
- Under the European Union's REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) scheme, the use of dichloromethane in paint strippers above a concentration of 0.1 per cent by weight is restricted to industrial facilities and certified professionals.

[104] Therapeutic Goods (Permissible Ingredients) Determination: https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[105] TGA prescribing medicines in pregnancy database: https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[106] Therapeutic Goods (Medicines Advisory Statements) Specification 2021: https://www.legislation.gov.au/Details/F2021L01888
[107] Database of Adverse Event Notifications (DAEN): https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[108] Public Chemical Registration Information System Search (PubCRIS): https://portal.apvma.gov.au/pubcris
[109] Safe Work Australia: https://www.safeworkaustralia.gov.au/

- Dichloromethane is prohibited from use in cosmetics in the EU under Annex II of the EU Cosmetics Regulations.[110]
- The United States Environmental Protection Agency[111] issued a ban in March 2019 on the use of dichloromethane in all paint and coating removers for consumer use.
- The Health Canada Cosmetic Ingredient Hotlist lists dichloromethane as "not permitted in aerosol products".
- Dichloromethane is included in Schedule 5 of the New Zealand Cosmetic Products Group Standard. Finished cosmetic products must not contain greater than 35% of a mixture of 1,1,1-trichloroethane and dichloromethane.

4.2 Ipflufenoquin

Proposal

The regulator, the Australian Pesticides and Veterinary Medicines Authority (APVMA), has submitted an application to enter a new fungicide, ipflufenoquin, into Appendix B of the Poisons Standard. Appendix B lists substances considered not to require control by scheduling.

CAS Number

1314008-27-9

Alternative names

2-[2-(7,8-difluoro-2-methylquinolin-3-yl)oxy-6-fluorophenyl]propan-2-ol

Applicant

Australian Pesticides and Veterinary Medicines Authority (APVMA)

Current scheduling

Ipflufenoquin is not included in the current Poisons Standard.

Proposed scheduling

Appendix B – New entry

SUBSTANCE	DATE OF ENTRY	REASON FOR LISTING	AREA OF USE
IPFLUFENOQUIN	<tba>	b	1.3

[110] Annex II EU Cosmetic Regulations: https://ec.europa.eu/growth/tools-databases/cosing/pdf/COSING_Annex II_v2.pdf

[111] EPA Final Rule on Methylene Chloride in Paint and Coating Removal for Consumer Use: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-rule-regulation-methylene-chloride-paint-and

REASON FOR LISTING: b – Use pattern restricts hazard.

AREA OF USE: 1.3 – Fungicide.

Application summary - reasons for proposal

- Ipflufenoquin is a novel, broad-spectrum fungicide proposed for use on berry and apple crops.
- It has not been previously considered by the APVMA but has been submitted for registration in South Korea, the United States of America, and the European Union. Ipflufenoquin has been approved in Japan since 2020.
- Based on toxicological data provided to the APVMA, ipflufenoquin does not appear to meet the factors for inclusion in the Schedules of the Poisons Standard.

Key uses / expected use

Fungicide

Australian regulations

- Ipflufenoquin does not appear in the TGA Ingredient Database.[112]
- There are no medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[113] that contain ipflufenoquin as an active ingredient.
- Ipflufenoquin is not included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[114] No. 3 of 2022.
- Ipflufenoquin does not appear in the TGA prescribing medicines in pregnancy database.[115]
- Ipflufenoquin does not appear in the Therapeutic Goods (Medicines Advisory Statements) Specification 2021.[116]
- Ipflufenoquin does not appear in the Public Chemical Registration Information System Search (PubCRIS).[117]

[112] TGA Ingredient Database https://www.ebs.tga.gov.au/
[113] ARTG database https://www.tga.gov.au/artg
[114] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[115] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[116] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[117] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris

International regulations

- As of January 2022, the United States' Environmental Protection Agency (EPA) has established tolerances for ipflufenoquin residues in or on almond crops and pome fruit.[118]
- The Canadian Pesticides and Pest Management database indicates that ipflufenoquin remains under evaluation.[119]
- Ipflufenoquin does not appear on the New Zealand Inventory of Chemicals (NZIoC).[120]

5. How to respond

Submissions must be provided by the closing date of **27 May 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 September 2022.

[118] Environmental Protection Agency (EPA), *Ipflufenoquin; Pesticide Tolerances*, United States Federal Register: https://www.federalregister.gov/documents/2022/03/01/2022-04264/ipflufenoquin-pesticide-tolerances
[119] Pesticide Product Information Database, Government of Canada: https://pest-control.canada.ca/pesticide-registry/en/active-ingredient-details.html?q=IPF
[120] New Zealand Inventory of Chemicals (NZIoC): https://www.epa.govt.nz/database-search/new-zealand-inventory-of-chemicals-nzioc/