Australian Government

Department of Health
Therapeutic Goods Administration

Publication of interim decisions amending, or not amending, the current Poisons Standard, June 2018

7 June 2018

Proposed amendments to the Poisons Standard referred to expert advisory committee

Subdivision 3D.2 of the *Therapeutic Goods Regulations 1990* (the Regulations) sets out the procedure to be followed in circumstances including where the Secretary receives an application under section 52EAA of the *Therapeutic Goods Act 1989* (the Act) to amend the current *Poisons Standard* and decides to refer the proposed amendment to an expert advisory committee.

Under regulation 42ZCZK, these procedures require (among other things) the Secretary to publish (in a manner the Secretary considers appropriate) a notice specifying the expert advisory committee to which the proposed amendment will be referred, the date of the meeting of the committee and details of the proposed amendment.

Pursuant to regulation 42ZCZK, the Secretary must 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. Such a notice relating to the interim decisions referred to herein was made available on the TGA website on 21 December 2017 and the opportunity to make submissions closed on 2 February 2018. Public submissions received on or before this closing date were published on the TGA website at Consultation: Proposed Amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS-ACMS meetings, March 2018 in accordance with subregulation 42ZCZL(3).

Under regulation 42ZCZN of the Regulations, the Secretary, after considering the advice or recommendation of the expert advisory committee, must (subject to regulation 42ZCZO) make an interim decision in relation to the proposed amendment. If the interim decision is to amend the current *Poisons Standard*, the Secretary must, in doing so, take into account the matters mentioned in subsection 52E(1) of the Act (including, for example, the risks and benefits of the use of a substance, and the potential for abuse of a substance) and the scheduling guidelines as set out in the *Scheduling Policy Framework for Medicines and Chemicals*.

Publication of decisions pursuant to regulations 42ZCZP of the Therapeutic Goods Regulations 1990

In accordance with regulation 42ZCZP, this notice gives effect to the Secretary's obligation to publish the interim decisions, the reasons for those decisions and the proposed date of effect of decisions made pursuant to regulation 42ZCZN

The interim decisions to which this notice relates include decisions made in respect to:

- scheduling proposals initially referred to the March 2018 meeting of the Advisory Committee on Medicines Scheduling (ACMS #23);

- scheduling proposals initially referred to the March 2018 meeting of the Joint meeting of the Advisory Committees on Chemicals and Medicines Scheduling (Joint ACCS-ACMS #18); and
- scheduling proposals initially referred to the March 2018 meeting of the Advisory Committee on Chemicals Scheduling (ACCS #22).

Also in accordance with regulation 42ZCZP of the Regulations, this notice invites interested persons to make submissions to the Secretary in relation to the interim decisions by the closing date.

Submissions must be received by close of business **5 July 2018.** See How to respond.

How to respond

Submissions must:

- be relevant to the proposed amendment, including whether or not you support the amendment/s;
- address matters mentioned in section 52E of the *Therapeutic Goods Act 1989;*
- be submitted by the closing date to medicines.scheduling@health.gov.au for substances referred to the ACMS or Joint ACMS-ACCS, or chemicals.scheduling@health.gov.au for substances referred to the ACCS. (Please include 'Proposed Amendments to the Poisons Standard (Medicines/Chemicals)' in the subject line of the email);
- ideally be no more than 3 pages; and
- be accompanied by a completed TGA Consultation submission coversheet (Microsoft Word, 65kb).

Submissions might also include:

- Suggested improvements; and/or
- An assessment of how the proposed change will impact on you. That is, what do you see as the likely benefits or costs to you (these may be financial or non-financial). If possible, please attempt to quantify these costs and benefits.

What will happen

All public submissions will be published on the TGA website Public submissions on scheduling matters, unless marked confidential or indicated otherwise in the submission cover sheet (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 on **5 July 2018**.

Privacy and your personal information

The TGA collects your personal information in this submission in order to:

- Contact you if the TGA wants to seek clarification of issues raised in your submission or to check whether you consent to certain information that you have provided being made publicly available.

- Help provide context about your submission (e.g. to determine whether you are an individual or a director of a company or representing an interest group).

The TGA will disclose your name and (if applicable) your designation/work title on the TGA Internet site (i.e. make this information publicly available) if you consent to the publication of your name on the TGA Internet site (please complete the cover sheet, see How to respond above). If at any point in time, you change your mind and wish for your personal information to be redacted then please contact the Scheduling Secretariat at medicines.scheduling@health.gov.au so that the pubic submissions can be updated accordingly.

Any text within the body of your submission that you want to remain confidential should be clearly marked 'IN CONFIDENCE' and highlighted in grey.

The Therapeutic Goods Administration (TGA) will not publish information it considers confidential, including yours/other individuals' personal information (unless you/they have consented to publication or it is required by law) or commercially sensitive information. Also, the TGA will not publish information that could be considered advertising or marketing (e.g. logos or slogans associated with products), information about any alleged unlawful activity or that may be defamatory or offensive.

Please do not include personal information about other individuals in the body of your submission. Personal information in this context means information or an opinion about an individual whose identity is apparent, or can reasonably be ascertained, from the information or opinion.

For general privacy information, go to https://www.tga.gov.au/privacy. The TGA is part of the Department of Health and the link includes a link to the Department's privacy policy and contact information if you have a query or concerns about a privacy matter.

Enquiries

Any questions relating to submissions should be directed by email to medicines.scheduling@health.gov.au (for substances referred to the ACMS or Joint ACCS-ACMS) or chemicals.scheduling@health.gov.au (for substances referred to the ACCS).

Contents

1. Advisory Committee on Medicines Scheduling (ACMS #23)

1.1 Diclofenac

Delegate's interim decision

The delegate's interim decision is to amend the Schedule 2 entry for diclofenac in the Poisons Standard to read as follows:

Schedule 2 – Amend Entry

DICLOFENAC when:

a) in divided preparations for oral use containing 12.5 mg or less of diclofenac per dosage unit in a pack containing 20 or less dosage units and labelled with a recommended daily dose of 75 mg or less of diclofenac; or

b) in preparations for dermal use containing 4 per cent or less of diclofenac **except** in preparations for dermal use containing 2 per cent or less of diclofenac or for the treatment of solar keratosis; or

c) in transdermal preparations for topical use containing 140 mg or less of diclofenac.

Proposed implementation date: 1 October 2018

The delegate considers the Committee's proposed implementation date of 1 October 2018 as being reasonable and appropriate in the circumstances.

Reasons:

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

- The delegate agrees with the Committee's advice that use of this substance creates the potential for a very slight increase in cardiovascular toxicity when compared to diclofenac 1% gel. However, noting that the daily dose is the same for both gels, the risk posed by the 2% gel is no greater than the risk posed by the 1% gel.
- The delegate agrees with the Committee' advice that there are a number of benefits of associated with having the 2% gel more accessible to consumers:
  - The 2016 Cochrane Systemic review demonstrates proven efficacy[1] at the proposed dose with adverse effect profile that is comparable to placebo and much reduced systemic toxicity compared to oral diclofenac;

[1] Derry, S., P. Conaghan, J. A. Da Silva, *et al*., Topical NSAIDs for chronic musculoskeletal pain in adults; 2016 *Cochrane Database Syst Rev* 4,Cd007400.

- Serious adverse events are rare and the likelihood of adverse effects with the topical product is lower than with oral products and is no greater than for the same daily dose using the 1% product.
- Use of the gel reduces use of other oral NSAIDs;
- Use of the gel results in significantly lower peak serum levels compared to oral products; and
- The 2% gel has the added advantage over the 1% gel because it only has to be used twice a day as opposed to four times a day. This improves likelihood of patient compliance and usability.

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

- Temporary (up to 3 weeks) relief of local pain and inflammation (swelling and redness) that may occur in mild forms of osteoarthritis of the knees and fingers.
- Topical use for mild pain associated with osteoarthritis in the fingers and knees.

c) the toxicity of a substance:

- similar to the 1% gel and known NSAID toxicity according to the instructions of use;
- has significantly lower peak serum levels compared to oral products; and
- there has been large use in the UK and New Zealand with no significant issues.

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

- daily dosage of 2% gel when used as indicated is the same as for the 1% gel;
- the potential for confusion between products can be effectively mitigated by appropriate labelling and packaging; and
- 2% diclofenac gel, labelling states 12 hourly, not to use for more than 3 weeks and to cease use after 7 days if condition gets worse or no better.

e) the potential for abuse of a substance:

- Does not appear to have an abuse potential.

Scheduling proposal

The pre-meeting scheduling proposal for diclofenac was published on the TGA website on 21 December 2017 at Consultation: Proposed Amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS-ACMS meetings, March 2018.

Background information for diclofenac

Referred scheduling proposal

An application was submitted to amend the Poisons Standard with respect to diclofenac. The application proposes to amend the Schedule 2 entry for diclofenac to exempt preparations for dermal use containing 2% or less of diclofenac from the Poisons Standard, except when labelled for the treatment of solar keratosis.

Scheduling application

The proposed amendments to the Poisons Standard are:

Schedule 2 – Amend Entry

DICLOFENAC when:

a) in divided preparations for oral use containing 12.5 mg or less of diclofenac per dosage unit in a pack containing 20 or less dosage units and labelled with a recommended daily dose of 75 mg or less of diclofenac;

b) in preparations for dermal use containing 4 per cent or less of diclofenac except in preparations for dermal use containing 2 per cent or less of diclofenac or for the treatment of solar keratosis; or

c) in transdermal preparations for topical use containing 140 mg or less of diclofenac.

The applicant's reasons for the proposal are:

- Dermal preparations containing 1% or less of diclofenac have been exempt from scheduling since February 2000. Diclofenac gel 2% (equivalent to diclofenac diethylammonium (DDEA) 2.32%) has been marketed in Australia as a Schedule 2 product for over 3 years. The date of first supply was June 2014.
- Globally, there is an accumulating history of use of the Diclofenac 2% gel formulation:
  - Diclofenac 2% gel was first registered in May 2011. As of 2017, 67 countries had received marketing approval for Diclofenac 2% gel.
  - Sales data indicate that from first marketing through to 31 July 2016, approximately 45.2 million patients have been exposed to the sponsor's Diclofenac 2% gel.
  - Diclofenac 2% gel is unscheduled and approved for general sale in two major markets – New Zealand (NZ) (authorised July 2013) and the United Kingdom (UK) (authorised 2013).
- The Advisory Committee on Medicines Scheduling (ACMS) reviewed a scheduling proposal to exempt Diclofenac 2% gel from scheduling in May 2014. The decision was to retain the Schedule 2 status. The reasons cited were:
  - The formulation had not been available for wider community use;
  - Lack of evidence of safety from the wider use in the community;
  - Potential for confusion arising from the different dosing regimen from the current (1%) product; and
  - In-pharmacy scheduling status in other markets such Switzerland, UK, Ireland and Canada.
- Significant changes have occurred since this prior submission:
  - There has been increased availability globally;
  - The Cochrane Collaboration has published new efficacy/safety reviews; and
  - There has been sufficient in-market use to enable a direct comparison of safety reporting data for the 1% and 2% strength gels.

- There is long standing prior precedence from other topical products to have the same active ingredients at different strengths in a general sales environment in Australia (e.g. rubefacient products containing methyl salicylate). These products are used for the same indication as diclofenac gel 2%, alleviating concerns about the potential for dose confusion.

- There is now sufficient additional safety information addressing the reasons cited by the ACMS in May 2014 for having retained the Schedule 2 status.

- Three recent Cochrane reviews, (Derry *et al.*, 2015, Derry *et al.*, 2016, Derry *et al.*, 2017) provide high quality evidence showing a lack of systemic safety problems with topical non-steroidal anti-inflammatory drugs (NSAIDs). The Cochrane reviews support the view that the lack of systemic problems makes topical NSAIDs particularly useful for those individuals unable to tolerate oral NSAIDs or for those in whom oral NSAIDs are contraindicated (e.g. due to older age). Thus unscheduled availability is highly beneficial due to the absence of systemic safety concerns.[2,3,4]

- Topical NSAIDs are universally recommended across international and national guidelines for knee and hand osteoarthritis, generally ahead of oral NSAIDs or opioids for pain relief, due to their superior safety profile (Rannou *et al.*, 2016).[5]

- Non-adherence to available pharmacological treatments is a problem that has the potential to impact on population health and expenditure (Laba *et al.*, 2013).[6] Importantly, when making decisions about the use of topical and oral NSAIDs, patients with osteoarthritis perceive medications that do not fit in with their lifestyle to be less effective than those that do (Carnes *et al.*, 2008).[7]

- The data provided within the application support the efficacy and safety of Diclofenac 2% gel when used as directed. The Diclofenac 2% gel formulation provides the same total daily dose of diclofenac as the DDEA 1.16% gel in fewer doses.

- The indications for use of Diclofenac 2% gel are the same as those for other topical analgesics currently available for general sale. Any potential risks with Diclofenac 2% gel are extremely low and are no different to those associated with DDEA 1.16% gel or other topical analgesics that are already available for general sale.

- The evidence, combined with favourable labelling provisions (name, indication, label colour and an in-pack Patient Information Leaflet), supports the proposal that Diclofenac 2% gel be down-scheduled from Pharmacy-only to general sales.

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[2] Derry, S., R. A. Moore, H. Gaskell, *et al.*, Topical NSAIDs for acute musculoskeletal pain in adults; 2015 *Cochrane Database Syst Rev* (6),CD007402.

[3] Derry, S., P. Conaghan, J. A. Da Silva, *et al.*, Topical NSAIDs for chronic musculoskeletal pain in adults; 2016 *Cochrane Database Syst Rev* 4,Cd007400.

[4] Derry, S., P. J. Wiffen, E. A. Kalso, *et al.*, Topical analgesics for acute and chronic pain in adults - an overview of Cochrane Reviews; 2017 *Cochrane Database Syst Rev* 5,Cd008609.

[5] Rannou, F., J.-P. Pelletier and J. Martel-Pelletier. Efficacy and safety of topical NSAIDs in the management of osteoarthritis: Evidence from real-life setting trials and surveys; 2016 *Seminars in Arthritis and Rheumatism* 45(4),S18-S21.

[6] Laba, T.-L., J.-a. Brien, M. Fransen, *et al.*, Patient preferences for adherence to treatment for osteoarthritis: the Medication Decisions in Osteoarthritis Study (MEDOS); 2013 *BMC Musculoskeletal Disorders* 14(1),160.

[7] Carnes, D., Y. Anwer, M. Underwood, *et al.*, Influences on older people's decision making regarding choice of topical or oral NSAIDs for knee pain: qualitative study; 2008 *BMJ : British Medical Journal* 336(7636),142-145.

Current scheduling status

Diclofenac is listed in Schedules 2, 3 and 4, as well as Appendices F and H of the Poisons Standard as follows:

Schedule 2

DICLOFENAC when:

a) in divided preparations for oral use containing 12.5 mg or less of diclofenac per dosage unit in a pack containing 20 or less dosage units and labelled with a recommended daily dose of 75 mg or less of diclofenac;

b) in preparations for dermal use containing 4 per cent or less of diclofenac **except** in preparations for dermal use containing 1 per cent or less of diclofenac or for the treatment of solar keratosis; or

c) in transdermal preparations for topical use containing 140 mg or less of diclofenac.

Schedule 3

DICLOFENAC in divided preparations for oral use containing 25 mg or less of diclofenac per dosage unit in a pack containing 30 or less dosage units except when included in Schedule 2.

Schedule 4

DICLOFENAC except:

a) when included in Schedule 2 or 3; or

b) in preparations for dermal use unless:

i) for the treatment of solar keratosis; or

ii) containing more than 4 per cent of diclofenac.

Appendix F, Part 3

Warning Statements: 101, 104

Appendix H

DICLOFENAC.

Scheduling history

The scheduling history for diclofenac in dermal preparations is outlined below.

In March 1981, diclofenac was first included in Schedule 4.

In February 1997, the National Drugs and Poisons Schedule Committee (NDPSC) rescheduled diclofenac from Schedule 4 to Schedule 2 in dermal preparations (creams) containing 1 per cent or less of diclofenac. This decision was based on the safety profile of a 1 per cent formulation and the then approved indications for use in readily recognised conditions (minor pain relief), which did not include treatment of solar keratosis.

In August 1999, the NDPSC decided that the scheduling of diclofenac in dermal preparations remained appropriate after considering recommendations from the Trans-Tasman Harmonisation Working Party to exempt diclofenac for dermal use.

In November 1999, the NDPSC deferred consideration of the scheduling of diclofenac in dermal preparations.

In February 2000, the NDPSC exempted dermal preparations of diclofenac from scheduling based on additional safety data.

In March 2011, following advice from the December 2010 ACMS meeting, the delegate included dermal preparations containing more than 1 per cent of diclofenac or preparations for the treatment of solar keratosis in Schedule 4.

In February 2012, following advice from the October 2011 ACMS meeting, the delegate rescheduled dermal preparations containing more than 1 per cent and up to 4 per cent or less of diclofenac to Schedule 2, except when for the treatment of solar keratosis. The delegate also confirmed that Schedule 4 remained appropriate for preparations containing more than 4 per cent of diclofenac, that preparations containing 1 per cent or less of diclofenac would remain unscheduled and that preparations for use in solar keratosis would remain in Schedule 4.

In February 2013, following advice from the October 2012 ACMS meeting, the delegate included transdermal preparations for topical use containing 140 mg or less of diclofenac in Schedule 2, with an implementation date of 1 May 2013.

In a final decision published in June 2013, the delegate considered a proposal to exempt diclofenac when presented in a transdermal drug delivery system containing 140 mg or less of diclofenac. The decision was that the scheduling was appropriate, as there was no clinical or marketing experience with this formulation in Australia, and Schedule 2 allows for access to professional advice at the time of purchase.

In July 2014, following the advice from the March 2014 ACMS meeting, the delegate decided that the scheduling of diclofenac remained appropriate and decided not to exempt dermal use preparations containing 2 per cent or less of diclofenac from scheduling. The delegate noted that a diclofenac 2 per cent topical solution is a Prescription Only Medicine in the United States of America.

Australian regulations

The Australian Register of Therapeutic Goods (ARTG) has 99 products listed that contain diclofenac, diclofenac diethylamine, diclofenac potassium and diclofenac sodium. The products marketed include topical preparations, immediate and modified realise capsules and tablets, eye drops and suppositories with varying strengths and quantities.

Diclofenac does not appear in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2018, as it is a scheduled ingredient and is not eligible for use in ARTG listed medicines.

In the last 30 years there have been 1935 reported cases of adverse events related to diclofenac in the Database of Adverse Events Notification (DAEN) - Medicines: 1194 cases with a single suspected medicine and 43 cases where death was a reported outcome.

According to the TGA Ingredient Database, diclofenac diethylamine is available for use as an:

- Active ingredient in: Biologicals, Export Only, Over The Counter, Prescription Medicines; and
- Excipient ingredient in: Biologicals, Devices, Prescription Medicines.

Diclofenac is not an approved active constituent with APVMA. One product had been registered with APVMA. However, this product was discontinued in November 1991.

International regulations

Canada

Health Canada regulates diclofenac as a prescription and over-the-counter medicine.

NZ

Ingredient	Conditions (if any)	Classification
Diclofenac	in preparations for the treatment of solar keratosis; **except** when specified elsewhere in this schedule; **except** in preparations for external use other than for the treatment of solar keratosis	Prescription
Diclofenac	in solid dose form in medicines containing 25 milligrams or less and more than 12.5 milligrams per dose form in packs containing not more than 30 tablets or capsules	Restricted
Diclofenac	in solid dose form in medicines containing 12.5 milligrams or less per dose form in packs containing not more than 30 tablets or capsules and with a recommended daily dose of not more than 75 milligrams	Pharmacy Only
Diclofenac	in preparations for external use other than for the treatment of solar keratosis	General Sale

United States of America (USA)

The USA Food and Drug Administration regulate diclofenac in varying dose forms as prescription medicines.

UK

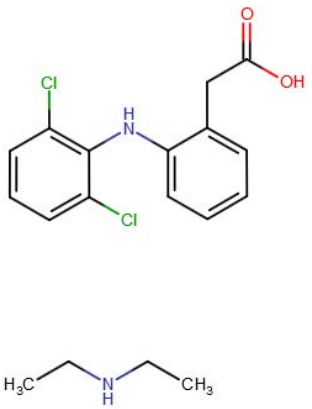
The UK regulates diclofenac as a:

- Prescription only medicine including varying strengths of immediate and modified release capsules and tablets, eye drops, ampoules, topical preparations, patches and suppositories;
- Pharmacy only medicine including cutaneous spray 4% and medical plaster; and
- General sales list medicine including emulgel 1.16% and 2.32% (active substance diclofenac diethylammonium).

Substance summary

In the 2% gel, diclofenac is present in its diethylammonium form [diclofenac diethylammonium (DDEA)].

Table 1.1A: Chemical information for DDEA

Property	DDEA
CAS number	78213-16-8
Chemical structure	
Molecular formula	$C_{14}H_{11}Cl_2NO_2.C_4H_{11}N$ (or $C_{18}H_{22}Cl_2N_2O_2$)
Molecular weight	369.3 g/mol
IUPAC and/or common and/or other names	diclofenac diethylammonium (DDEA); Diclofenac diethylamine; 2-((2,6-Dichlorophenyl)amino)benzeneacetic acid, compd. with N-ethylethanamine; *N*-ethylethanaminium{2-[(2,6-dichlorophenyl)amino]phenyl}acetate; Benzeneacetic acid, 2-((2,6-dichlorophenyl)amino)-, compd. with N-ethylethanamine (1:1); *N*-Ethylethanamine 2-[(2,6-dichlorophenyl)amino]
Action and use	Cyclo-oxygenase (COX) inhibitor; analgesic; anti-inflammatory
Description	A white to light beige, crystalline powder
Solubility	Sparingly soluble in water and in acetone; freely soluble in ethanol (96%) and in methanol; practically insoluble in 1M sodium hydroxide

Pre-meeting public submissions

Four (4) public submissions were received, two (2) in support and two (2) opposed.

The main points provided in support of the amendment were:

- Topical diclofenac is a safe and effective analgesic. The safety profile of 2% diclofenac gel is comparable to the 1% gel and can be supplied with reasonable safety without access to a health professional.

- The proposed 2% diclofenac gel requires less frequent dosing than the unscheduled 1% gel and will be easily differentiated from each other by labelling. The less frequent application will also lead to better adherence and better outcomes.
- Since the last consideration to exempt 2% diclofenac gel from scheduling in May 2014, new evidence highlights the safety from wider use. Recent TGA reviews have also shown that topical diclofenac has a well-characterised and favourable safety profile.
- There is no evidence of dependence or abuse.
- 2% diclofenac gel is unscheduled in NZ and the UK and international misuse is rare.
- Exempting 2% diclofenac gel from scheduling does not affect regulation of the product. Products will continue to be regulated in relation to its manufacturing, composition, packaging and advertising. The only change will be consumer access.

The main points provided in opposition of the amendment were:

- The TGA's full safety review of diclofenac in 2013 concluded that a conservative approach for topical diclofenac products is warranted. Further, research literature could not be located where the safety of topical 3% diclofenac was specifically examined.
- The Australian Product Information for topical 3% diclofenac makes reference to serious systemic side effects.
- Concomitant administration of diclofenac gel with oral NSAIDs or aspirin may result in increased adverse NSAID effects. Guidelines for prescribing indicate only one non-aspirin NSAID should be used at any time.
- Given the up-scheduling of combination codeine products, consumers will be seeking alternative products for relief of pain and consultation in a pharmacy would be appropriate to ensure quality use of medicines.
- The dosage guidelines for 2% diclofenac gel are different to 1% gel. The 2% concentration gel is applied half as often. Having potentially two types of unscheduled products available at different strengths increases the risk of medicine overuse and associated risks.
- Risks associated with 2% diclofenac gel are best mitigated with consumers having discussions regarding the safe and appropriate use of these medicines with pharmacy staff.
- Based on currently available information and evidence, the proposal of exempting dermal diclofenac from 1% to 2% is not supported.

The public submissions will be made available on the TGA website.

Summary of ACMS advice to the delegate

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

Schedule 2 – Amend Entry

DICLOFENAC when:

a) in divided preparations for oral use containing 12.5 mg or less of diclofenac per dosage unit in a pack containing 20 or less dosage units and labelled with a recommended daily dose of 75 mg or less of diclofenac;

b) in preparations for dermal use containing 4 per cent or less of diclofenac **except** in preparations for dermal use containing ~~1~~**2** per cent or less of diclofenac or for the treatment of solar keratosis; or

c) in transdermal preparations for topical use containing 140 mg or less of diclofenac.

The committee also provided the following comments regarding the regulation of products including diclofenac gel:

- That the different strength unscheduled packs of diclofenac should be well differentiated;
- Undertake a literature review and publish a consultation for updates to Required Advisory Statements for Medicine Labels (RASML); and
- Amend the Patient Information leaflet to include the risk of use in patients with cardiovascular disease (perhaps through the next RASML update).

The committee also recommended an implementation date of **1 October 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance.

The reasons for the advice included:

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

- Risks: a potential for a very slight increase in cardiovascular toxicity. However, it is the same for the 1% gel, which is also exempt.
- Benefits:
  - Proven efficacy (Derry et al., 2016[8] Cochrane Systematic Review) at the proposed dose with adverse effect profile that is comparable to placebo and much less (but not no) systemic toxicity compared to oral diclofenac;
  - Reduces use of other oral NSAIDs; and
  - Improved adherence – twice a day vs four times a day.
  - Serious adverse events are rare and the likelihood of adverse effects with the topical product is lower than with oral products.

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

- Temporary (up to 3 weeks) relief of local pain and inflammation (swelling and redness) that may occur in mild forms of osteoarthritis of the knees and fingers.
- Topical use for mild pain associated with osteoarthritis in the fingers and knees.

[8] Derry, S., P. Conaghan, J. A. Da Silva, *et al*., Topical NSAIDs for chronic musculoskeletal pain in adults; 2016 *Cochrane Database Syst Rev* 4,Cd007400.

c) the toxicity of a substance:

- As per 1% gel and known NSAID toxicity according to the instructions of use.

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

- The two products (2% and 1% gel) are insufficiently differentiated. Patient Information Leaflet should mention slight risk of cardiovascular toxicity as per oral diclofenac.
- 2% diclofenac gel, labelling states 12 hourly, not to use for more than 3 weeks and to cease use after 7 days if condition gets worse or no better.

e) the potential for abuse of a substance:

- Does not appear to have an abuse liability.

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

- Nil.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACMS advice;
- Public submissions received;
- Scheduling Policy Framework (SPF 2018); and
- Section 52E (1) of the *Therapeutic Goods Act 1989*, in particular: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance.

1.2 Cannabidiol, cannabis and tetrahydrocannabinols

Delegate's interim decision

The delegate's interim decision is to amend the Schedule 4 entry for cannabidiol, and the Schedule 8 and Appendix K entries for tetrahydrocannabinols and cannabis in the Poisons Standard to read as follows:

Schedule 4 Entry

CANNABIDIOL in preparations for therapeutic use where:

a) cannabidiol comprises 98 per cent or more of the total cannabinoid content of the preparation; and

b) any cannabinoids, other than cannabidiol, must be only those naturally found in cannabis and total 2 per cent or less of the cannabinoid content of the preparation.

Schedule 8

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

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

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

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

except when:

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

ii) in hemp seed oil, containing 50 mg/kg or less of tetrahydrocannabinols when labelled with either of the following warning statements:

(A) Not for internal use; or

(B) Not to be taken; or

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

iv) cannabidiol when included in Schedule 4.

Schedule 8

CANNABIS (including seeds, extracts, resins and the plant, and any part of the plant)

when prepared or packed for human therapeutic use, when:

a) cultivated or produced, or in products manufactured[9], in accordance with the *Narcotic Drugs Act 1967*; and/or

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

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

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

except:

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

ii) cannabidiol when included in Schedule 4; or

iii) when separately specified in the NABIXIMOLS entry in this Schedule; or

iv) when in hemp seed oil for purposes other than internal human therapeutic use containing 50 mg/kg or less of cannabinoids.

Appendix K

CANNABIS **except** cannabidiol when included in Schedule 4.

TETRAHYDROCANNABINOLS **except** cannabidiol when included in Schedule 4.

Proposed implementation date: 1 October 2018

The delegate considers the Committee's proposed implementation date of 1 October 2018 as being reasonable and appropriate in the circumstances.

Reasons:

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

- the overall risks and benefits remain the same as when last considered; and
- the known risks with drug interactions and potential to affect liver function reinforce need to be a prescription medicine.

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

- as the substance should be used under medical guidance due to potential drug interactions and effect on liver function it should be clear that it is a prescription medicine and what constitutes a Schedule 4 vs Schedule 8 substance.

[9] 'Cultivation', 'production' and 'manufacture' have the same meaning as in the *Narcotic Drugs Act 1967*

c) the toxicity of a substance:

- there is evidence of drug interactions and an effect on liver function.

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

- providing clarity to assist labelling and packaging.

e) the potential for abuse of a substance:

- little potential for abuse which reinforces Schedule 4 vs Schedule 8.

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

- This amendment is to clarify the entry following its implementation and does not seek to change the original scheduling decisions in a substantive manner.
- Clarification of these entries is necessary to prevent their inadvertent or deliberate misinterpretation resulting in harm through Schedule 8 products being treated as Schedule 4 products, including not obtaining State authority to prescribe, and increased potential for diversion/misuse because of less restrictive storage and recording requirements.

Scheduling proposal

The pre-meeting scheduling proposal for cannabidiol, cannabis and tetrahydrocannabinols was published on the TGA website on 21 December 2017 at Consultation: Proposed Amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS-ACMS meetings, March 2018.

Background information for cannabidiol, cannabis and tetrahydrocannabinols

Referred scheduling proposal

The delegate of the Secretary proposed an amendment to the Schedule 4 entry of cannabidiol, Schedule 8 entry of tetrahydrocannabinols and the Appendix K entries of cannabis and tetrahydrocannabinols (THCs) to clarify the meaning of the cannabidiol Schedule 4 entry in the Poisons Standard.

Scheduling application

The proposed amendments to the Poisons Standard are reflected below:

> **Schedule 4** CANNABIDIOL in preparations for therapeutic use ~~containing 2 per cent or less of other cannabinoids found in cannabis~~ in which:
>
> a) cannabidiol comprises at least 98 per cent of the total cannabinoid content of the preparation; and
>
> b) any other cannabinoids present are only those naturally found in cannabis, and are present only as unavoidable impurities in the cannabidiol component of the preparation.

Schedule 8

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

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

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

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

except when:

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

ii) in hemp seed oil, containing 50 mg/kg or less of tetrahydrocannabinols when labelled with either of the following warning statements:

(A) Not for internal use; or

(B) Not to be taken; or

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

iv) separately specified in Schedule 4.

Appendix K

CANNABIS **except** when included in Schedule 4.

(or CANNABIS in any form **except** the alkaloid cannabidiol)

TETRAHYDROCANNABINOLS **except** when included in Schedule 4.

(or TETRAHYDROCANNABINOLS in any form **except** the alkaloid cannabidiol).

The reasons for the proposed amendments are:

- The current schedule entry for cannabidiol is causing ongoing confusion. This amendment seeks to clarify the schedule entry.
- The proposed amendment is to further refine the scheduling delegate's final decision on cannabis and tetrahydrocannabinols and cannabidiol (published on 31 May 2017).
- To specify that cannabidiol is not considered likely to cause sedation.
- To identify cannabis and THCs as forming part of the '*other cannabinoid*' component in the cannabidiol Schedule entry.

Scheduling status at time of referral

Cannabidiol was specifically listed in Schedules 4 and 8 of the Poisons Standard October 2017 as follows:

> **Schedule 4**
>
> CANNABIDIOL in preparations for therapeutic use containing 2 per cent or less of other cannabinoids found in cannabis.
>
> **Schedule 8**
>
> # NABIXIMOLS (botanical extract of *Cannabis sativa* which includes the following cannabinoids: tetrahydrocannabinols, cannabidiol, cannabinol, cannabigerol, cannabichromene, cannabidiolic acid, tetrahydrocannabinolic acids, tetrahydrocannabivarol, and cannabidivarol, where tetrahydrocannabinols and cannabidiol (in approximately equal proportions) comprise not less than 90 per cent of the total cannabinoid content) in a buccal spray for human therapeutic use.
>
> **Index**
>
> CANNABIDIOL
> cross reference: CANNABIS, NABIXIMOLS
>
> Schedule 4

Related compounds cannabis and tetrahydrocannabinols are listed in Schedules 8 and 9 and Appendices D and K of the Poisons Standard as follows:

> **Schedule 8**
>
> # CANNABIS (including seeds, extracts, resins and the plant, and any part of the plant) when prepared or packed for human therapeutic use, when:
>
> a) cultivated or produced, or in products manufactured[10], in accordance with the *Narcotic Drugs Act 1967*; and/or
>
> b) for use in products manufactured in accordance with the *Narcotic Drugs Act 1967*; and/or
>
> c) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the *Therapeutic Goods Act 1989*; and/or
>
> d) in therapeutic goods supplied in accordance with the *Therapeutic Goods Act 1989*,
>
> **except** when:
>
> i) it is a product to which item 4, 8, 10, 11 or 12 of Schedule 5A to the *Therapeutic Goods Regulations 1990* applies; or
>
> ii) separately specified in Schedule 4; or
>
> iii) separately specified in the NABIXIMOLS entry in this Schedule; or

[10] 'Cultivation', 'production' and 'manufacture' have the same meaning as in the *Narcotic Drugs Act 1967*

iv) in hemp seed oil for purposes other than internal human therapeutic use containing 50 mg/kg or less of cannabinoids.

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

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

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

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

except when:

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

ii) in hemp seed oil, containing 50 mg/kg or less of tetrahydrocannabinols when labelled with either of the following warning statements:

(A) Not for internal use; or

(B) Not to be taken; or

iii) in products for purposes other than for internal human use containing 50 mg/kg or less of tetrahydrocannabinols; or

iv) separately specified in the NABIXIMOLS entry in this Schedule.

Schedule 9

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

a) when separately specified in these Schedules; or

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

c) in hemp seed oil for purposes other than internal human use containing 50 mg/kg or less of cannabinoids.

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

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

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

c) in hemp seed oil, containing 50 mg/kg or less of tetrahydrocannabinols when labelled with either of the following warning statements:

i) Not for internal use; or

ii) Not to be taken; or

d) in products for purposes other than internal human use containing 50 mg/kg or less of tetrahydrocannabinols.

Appendix D, Item 1

CANNABIS for human use.

TETRAHYDROCANNABINOLS for human use.

Appendix K

CANNABIS

TETRAHYDROCANNABINOLS

Pending scheduling changes as of 1 June 2018

Following a previous final decision made by a delegate of the Secretary and published on the TGA website on 31 May 2017, on 1 June 2018, the abovementioned entries will be amended to read as follows:

Schedule 9

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

a) when separately specified in these Schedules; or

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

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

i) Not for internal use; or

ii) Not to be taken.

Schedule 8

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

a) cultivated or produced, or in products manufactured[11], in accordance with the *Narcotic Drugs Act 1967*; and/or

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

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

[11] 'Cultivation', 'production' and 'manufacture' have the same meaning as in the *Narcotic Drugs Act 1967*

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

except when:

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

ii) separately specified in Schedule 4; or

iii) separately specified in the NABIXIMOLS entry in this Schedule.

Schedule 9

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

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

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

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

i) Not for internal use; or

ii) Not to be taken.

Schedule 8

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

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

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

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

except when:

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

ii) separately specified in the NABIXIMOLS entry in this Schedule.

Schedule 4

CANNABIDIOL in preparations for therapeutic use containing 2 per cent or less of total other cannabinoids found in cannabis.

Index

CANNABICHROMENE
cross reference: NABIXIMOLS, CANNABIS, TETRAHYDROCANNABINOLS

CANNABIDIOL
cross reference: NABIXIMOLS, CANNABIS, TETRAHYDROCANNABINOLS

CANNABIDIOLIC ACID
cross reference: NABIXIMOLS, CANNABIS, TETRAHYDROCANNABINOLS

CANNABIDIVAROL
cross reference: NABIXIMOLS, CANNABIS, TETRAHYDROCANNABINOLS

CANNABIGEROL
cross reference: NABIXIMOLS, CANNABIS, TETRAHYDROCANNABINOLS

CANNABINOIDS
cross reference: NABIXIMOLS, CANNABIS, TETRAHYDROCANNABINOLS

CANNABINOL
cross reference: NABIXIMOLS, CANNABIS, TETRAHYDROCANNABINOLS

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

TETRAHYDROCANNABINOLIC ACID
cross reference: NABIXIMOLS, TETRAHYDROCANNABINOLS, CANNABIS

TETRAHYDROCANNABINOLS
cross reference: CANNABIS, HEMP SEED OIL, NABIXIMOLS

TETRAHYDROCANNABIDIVAROL
cross reference: NABIXIMOLS, TETRAHYDROCANNABINOLS, CANNABIS

Scheduling history

In February 2009, cannabidiol (CBD) was discussed by the National Drug and Poisons Scheduling Committee (NDPSC) as a part of a consideration of THC and a THC containing product, which led to the creation of the nabiximols entry (June and October 2009).

While the focus of the February 2009 meeting item was on the classification of THC, a number of public submissions received were regarding the availability of the product which contains both THC and CBD. It was noted that it was difficult to give approval to special access scheme applications for medications containing CBD as it was considered a Schedule 9 substance. However, access would be granted if CBD was placed in Schedule 8 for therapeutic use. This scheduling consideration was to be discussed at the June 2009 meeting.

In June 2009, following further research regarding the product, the NDPSC decided that a Schedule 8 entry needed to exempt only the formulation from Schedule 9 rather than the 'substance' and therefore created the Schedule 8 entry for *Cannabis sativa* extract, listing the individual cannabidiols and restricting its presentation to buccal sprays for therapeutic use.

In October 2009, the NDPSC considered the scheduling of nabiximols after it was established that the United States of America Adopted Names Council had designated 'nabiximols' as the approved non-proprietary name for an extract of *Cannabis sativa.* This extract contained THC and CBD as major components and related cannabinoids and non-cannabinoid components alpha- and trans-caryophyllenes as minor components (i.e. the specific THC and CBD formulation considered appropriate for inclusion in Schedule 8 by the June 2009 meeting). As a result of this change in the US, the NDPSC amended Schedule 8 to refer to nabiximols instead of *Cannabis sativa*.

In November 2014, the ACMS considered the scheduling of cannabidiol. The committee recommended to the scheduling delegate that cannabidiol, including extracts of *Cannabis sativa*, and including preparations of up to 2% of cannabinoids, including cannabidivarin (CBDV) for therapeutic use, be included in Schedule 4. The reasons for the recommendation included:

- The condition that cannabidiol treats (the therapeutic use) requires diagnosis, management and monitoring under an appropriate medical practitioner.
- Cannabidiol has a safety profile which is consistent with a Schedule 4 listing.
- There is low risk of misuse or abuse as cannabidiol does not possess psychoactive properties.

In May 2016, after extensive consultation, the scheduling delegate agreed with the committee recommendations and provided further reasons and clarification of the decision that included:

- The schedule entry needs to acknowledge that there is no pure form of cannabidiol currently available. However, low levels of impurities found in some cannabidiol products are not clinically significant and the scheduling entry should reflect this by allowing cannabinoids up to 2 %.
- The entry allows for, but does not specify, any particular non-active cannabis impurity/ies to be within the 'up to 2%'.
- The substances that comprise the 'up to 2%' must be substances found in cannabis. They cannot be synthetic cannabinoids.
- The entry does not preclude the cannabidiol and/or any other cannabinoids being derived from natural sources or made artificially, consistent with the interpretation of the schedules.
- An amendment to Appendix D was not supported as the criteria are not met. It is considered that it is the medical condition for which CBD may be used which requires treatment by a specialist. Cannabidiol itself has no particular attributes that require it to be included in Appendix D. Scope of practice will ensure the appropriate prescribing of cannabidiol, rather than scheduling.

As a result, a Schedule 4 entry for cannabidiol was created, and the Schedule 9 entry for THC and their alkyl homologues was amended to exempt the new Schedule 4 entry for cannabidiol.

In November 2016, the Joint Advisory Committee on Medicines and Chemicals Scheduling (Joint ACMS-ACCS) further considered cannabidiol to improve the clarity of the entry with regards to the component cannabinoids found in cannabis. On 31 May 2017 the final decision and reasons was published. Amendments were made to the Schedule 8 and 9 entries for cannabis and tetrahydrocannabinols, and the Schedule 4 entry for cannabidiol. The amendment to the cannabidiol Schedule 4 entry (inclusion of the word '*total*' in relation to the other cannabinoids found in cannabis) was made to improve the clarity of the cannabidiol entry.

Australian regulations

On the Australian Register of Therapeutic Goods (ARTG), there is one product containing cannabidiol which has been approved for export only.

There is no reference to cannabidiol, cannabis or THC in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2018 as they are scheduled ingredients, and are not eligible for use in ARTG listed medicines.

According to the TGA Ingredient Database, cannabidiol is available for use as an Active Ingredient in Export Only and Prescription Medicines, and there is no reference to cannabis or THC.

In the last 30 years, in the Database of Adverse Events Notification (DAEN) - Medicines:

- There have been 2 reported cases of adverse events related to cannabidiol: 1 case with a single suspected medicine and no cases where death was a reported outcome;
- There have been 77 reported cases of adverse events related to cannabis: 77 cases with a single suspected medicine and 1 case where death was a reported outcome; and
- There have been no reported cases of adverse events related to THC.

International regulations

- **New Zealand:** Cannabidiol is classified as a Class B1 Controlled drug and Prescription Medicine and cannabis and THC are classified as a Class C1 Controlled Drugs.
- **United States of America (USA):** In the USA, 13 states have statutes recognising CBD for medical use, 23 states have statutes recognising 'medicinal marijuana'.
- **European Union:** The European Medicines Agency approved CBD for certain medical uses (GvHD, Dravet syndrome, Lennox-Gastaut syndrome, perinatal asphyxia) and THC for the treatment of pain and spasticity.
- **Canada:** Cannabidiol and THC are classified as a Schedule II medicine.

Substance summary

Cannabis

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

Cannabis contains about 60 cannabinoids, of which the main active constituent is delta-9-tetrahydrocannabinol. Delta-9-tetrahydrocannabinol reportedly has anti-emetic properties, and has been associated with claims relating to use for the control of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional anti-emetics. Another active cannabinoid present in Cannabis is cannabidiol, which is associated with claims relating to use as an analgesic, anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, anti-oxidant and anti-psychotic.

Nabiximols is a specific extract of *Cannabis sativa* which contains a range of cannabinoids, of which THC and cannabidiol, in approximately equal proportions, comprise not less than 90% of the total cannabinoid content. Nabiximols are registered for use in Australia as a buccal spray preparation as an adjunctive treatment for the symptomatic relief of neuropathic pain associated with multiple sclerosis in adults.

Nabilone is a synthetic cannabinoid used as an anti-emetic in the treatment of nausea and vomiting caused by chemotherapy and also for patients who are not responsive to conventional anti-emetic treatments.

Hemp seed oil as defined in Part 1 Interpretation, Paragraph (1) of the Poisons Standard is the oil obtained by cold expression from the ripened fruits (seeds) of *Cannabis sativa*. Hemp oil is

distinct from hemp seed oil and includes extracts from the flowering tops or leaves or any other part of the Cannabis plant other than the ripened fruit (seeds).

Information in the public domain, including websites and literature articles[12] report cannabinoids are not synthesised within the hemp seed. However, traces of delta-9-tetrahydrocannabinol and cannabidiol contamination of the seed may occur due to residual contamination of the outside of the seed coat, even under good agricultural/manufacturing practice. Rigorous cleaning methods, including washing, sieving and shelling, may help reduce or remove any cannabinoid contamination of seeds.

Reported gas chromatography (GC) analytical composition data of hemp seed oil (variety Fedora-19) from Leizer, *et al.*, (2000) includes significant portions of polyunsaturated fatty acids such as linoleic acid, oleic acid, stearic acid eichosanoic acids and palmitic acid, with more than 80% of the content being unsaturated fatty acids. Other trace compounds reported include Vitamin E (tocopherols), β-sitosterol, and terpenes (e.g. myrcene and caryophyllene) and salicylates.

Given this information, hemp seed oil products should not contain significant amounts of cannabinoids. The presence of cannabinoids in hemp seed oil is considered to arise from either a contamination or adulteration, rather than to be naturally occurring.

Cannabidiol

Cannabidiol is a cannabinoid compound which occurs naturally in *Cannabis sativa* plants. The pharmacology of cannabidiol is complex and has been well characterised *in vitro*.

Some cannabinoid compounds work by binding to the cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) receptors in the brain. Cannabidiol does not activate CB1 and CB2 receptors directly. However, it has effects on many other 'signalling' systems and can be considered a 'multi-target' drug. Some of the effects of cannabidiol may be attributed to inhibition of the inactivation of endocannabinoids, such as anandamide. Other effects may be related to the chemical properties of the compound as opposed to pharmacodynamic effects. For example, it is thought that the presence of two hydroxyl groups enables cannabidiol to have an anti-oxidant action.

There is evidence that cannabidiol affects serotonin receptors (5HT1A), adenosine uptake, nuclear receptors of the peroxisome proliferator-activated receptors (PPAR) family and other pharmacological targets. The pharmacological targets of cannabidiol include receptors, ion channels, enzymes and cellular uptake processes.

There are reports that cannabidiol possesses anti-proliferative, pro-apoptotic effects and inhibits cancer cell migration, adhesion and invasion. Evidence is also accumulating that there are positive effects of cannabidiol in the vasculature, where cannabidiol may induce vasorelaxation.

Information about the pharmacokinetics of the substance in humans is also accumulating. Oral absorption is slow and unpredictable relative to other routes of administration, possibly due to the chemical's poor water solubility. There is significant first pass metabolism where the concentration of ingested cannabidiol is greatly reduced before it is absorbed into systemic circulation, and the overall oral bioavailability may be as low as 6%. Other sources suggest an oral bioavailability of between 12 and 19%. Oromucosal and sublingual delivery, through sprays and lozenges, results in less variability with similar overall bioavailability.

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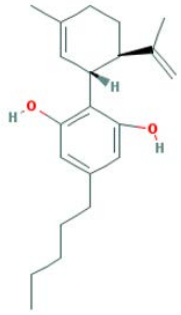
[12] P1042 - Low THC Hemp Seeds as Food and Leizer, C. *et al*., The Composition of Hemp Seed Oil and Its Potential as an Important Source of Nutrition (pdf,145kb), J. Nutraceuticals, Functional & Medical Foods 2000 2(4) 35 - 53

The distribution of cannabidiol is governed by its high lipophilicity and there is rapid distribution to the brain, adipose tissue and other organs. It is also highly protein bound.

Like most cannabinoids, cannabidiol is extensively metabolised in the liver by cytochrome P450 enzymes, predominantly the CYP3A and CYP2C series. The terminal half-life is estimated to be 18-32 hours, although earlier work suggested a much shorter half-life of only 9 hours.

Table 1.2A: Chemical information of cannabidiol

Property	Cannabidiol
CAS number	13956-29-1
Chemical structure	
Molecular formula	$C_{21}H_{30}O_2$
Molecular weight	314.469 g/mol
IUPAC and/or common and/or other names	2-[(1*R*,6*R*)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol (IUPAC)

Tetrahydrocannabinol

THC is one of at least 113 cannabinoids identified in cannabis and is the principal psychoactive constituent of cannabis.

The THC effects result from its partial agonist activity at the cannabinoid receptor CB1 located mainly in the central nervous system, and the CB2 receptor mainly expressed in cells of the immune system. The psychoactive effects of THC are primarily mediated by the activation of cannabinoid receptors, which result in a decrease in the concentration of the second messenger molecule cAMP through inhibition of adenylate cyclase.

Pre-meeting public submissions

One (1) public submission was received which opposed the proposal.

The main points provided in opposition of the amendment were:

- The key area of confusion is in respect to the cannabidiol content of the preparation, versus its proportion to other cannabinoids. Interpretations have included 98% of the preparation must be cannabidiol in contrast to 98% of the total cannabinoids in the preparation must be cannabidiol.

- The proposed Schedule 4 cannabidiol entry amendment introduces additional ambiguity, including:
  - The use of the word 'other' in point b implies that the cannabidiol itself may not be subject to the requirement of being 'naturally found in cannabis'; and
  - The introduction of the term 'unavoidable impurities' with regards to other cannabinoids present introduces ambiguity and subjectivity in what, under point a, had been a quantitative measure i.e. that cannabinoids other than cannabidiol can only represent up to 2% of the total cannabinoid content.
- Although it is self-explanatory that tetrahydrocannabinol is a cannabinoid, it is not clear how or where tetrahydrocannabinols are '*included*' or '*specified*' in Schedule 4. This can be addressed by specifically making reference to tetrahydrocannabinol in the cannabidiol entry, and also by cross referencing tetrahydrocannabinols to cannabidiol in the Index of the Poisons Standard. This would assist in comprehension of the proposed amendments to the tetrahydrocannabinol entries in Appendix K and Schedule 8.

The public submission will be made available on the TGA website.

Summary of ACMS advice to the delegate

The committee recommended that the Schedule 4 entry for cannabidiol, the Schedule 8 entry for tetrahydrocannabinols and the Appendix K entries of tetrahydrocannabinols and cannabis be amended in the Poisons Standard as follows:

Schedule 4 – Amend Entry

CANNABIDIOL in preparations for therapeutic use ~~containing 2 per cent or less of other cannabinoids found in cannabis~~ where:

a) cannabidiol comprises 98 per cent or more of the total cannabinoid content of the preparation; and

b) any cannabinoids, other than cannabidiol, must be only those naturally found in cannabis and total 2 per cent or less of the cannabinoid content of the preparation.

Schedule 8 – Amend Entry

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

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

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

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

except when:

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

ii) in hemp seed oil, containing 50 mg/kg or less of tetrahydrocannabinols when labelled with either of the following warning statements:

(A) Not for internal use; or

(B) Not to be taken; or

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

iv) the alkaloid cannabidiol when included in Schedule 4.

Schedule 8 – Amend Entry

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

a) cultivated or produced, or in products manufactured[13], in accordance with the *Narcotic Drugs Act 1967*; and/or

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

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

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

except:

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

ii) ~~separately specified in Schedule 4~~ the alkaloid cannabidiol when included in Schedule 4; or

iii) when separately specified in the NABIXIMOLS entry in this Schedule; or

iv) when in hemp seed oil for purposes other than internal human therapeutic use containing 50 mg/kg or less of cannabinoids.

Appendix K – Amend Entry

CANNABIS **except** the alkaloid cannabidiol when included in Schedule 4.

TETRAHYDROCANNABINOLS **except** the alkaloid cannabidiol when included in Schedule 4.

The committee also recommended an implementation date of **1 October 2018**.

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

[13] 'Cultivation', 'production' and 'manufacture' have the same meaning as in the *Narcotic Drugs Act 1967*

The reasons for the advice included:

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

- Benefit – clarity of entry meaning

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

- See point (f).

c) the toxicity of a substance:

- See point (f).

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

- See point (f).

e) the potential for abuse of a substance:

- See point (f).

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

- This consideration is about clarification only and does not seek to change the original scheduling decisions in a substantive manner.
- Clarification of these entries is necessary to prevent their inadvertent or deliberate misinterpretation resulting in harm through Schedule 8 products being treated as Schedule 4 medicines, including not obtaining State authority to prescribe, and increased potential for diversion/misuse because of less restrictive storage and recording requirements.

Delegate's considerations

In making this decision, I have considered the following:

- Scheduling proposal;
- ACMS advice;
- Public submission received;
- Scheduling Policy Framework (SPF 2018); and
- Section 52E(1) of the *Therapeutic Goods Act 1989* in particular: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

1.3 Fluticasone

Delegate's interim decision

The delegate's interim decision is to amend the Schedule 2 entry for fluticasone in the Poisons Standard to read as follows:

Schedule 2 – Amend Entry

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

Proposed implementation date: 1 October 2018

The delegate considers the Committee's proposed implementation date of 1 October 2018 as being reasonable and appropriate in the circumstances.

Reasons:

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

- Benefits:
  - Over 30 years' experience with this agent in Australia including 16 years non-prescription experience.
  - Intranasal corticosteroids such as fluticasone are well-established as recommended agents for effective long-term management of symptoms of allergic rhinitis with favourable long-term use safety profile.
  - Long-term safety profile established from clinical trials and extensive post-marketing data with insignificant systemic absorption of fluticasone from intranasal administration or any portion of dose that is swallowed.
- Risks:
  - There is no difference in the risks of the substance by allowing more doses per pack.

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

- Symptomatic treatment and prophylaxis of allergic rhinitis in adults and children over 12 years.
- Australian prevalence of allergic rhinitis ranges from 12-26% (AIHW analysis of ABS National Health Survey, 2014-15).

c) the toxicity of a substance:

- High tolerability and safety with low frequencies of adverse events reported in clinical trials and post-marketing.

- Larger pack size will not affect the toxicity.

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

- Removal of actuation limit would allow the supply of a larger number of doses per occasion of supply to treat a chronic condition, providing up to 6-months of treatment, which will enhance adherence, improve symptom control and quality of life, and reduce medicine and healthcare resource costs.

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

- Minimising barriers to compliance with intranasal corticosteroids is of benefit.
- Enhanced consumer access and treatment continuity.

Scheduling proposal

The pre-meeting scheduling proposal for fluticasone was published on the TGA website on 21 December 2017 at Consultation: Proposed Amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS-ACMS meetings, March 2018.

Background information for fluticasone

Referred scheduling proposal

An application was submitted to amend the Poisons Standard with respect to fluticasone. The application proposes to amend the Schedule 2 entry for fluticasone to remove the limit of 200 actuations.

Scheduling application

The application proposed the following amendments to the Poisons Standard:

Schedule 2 – Amend Entry

FLUTICASONE in aqueous nasal sprays delivering 50 micrograms or less of fluticasone per actuation when the maximum recommended daily dose is no greater than 400 micrograms ~~and when packed in a primary pack containing 200 actuations or less,~~ for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

The applicant's reasons for the request are:

- There is substantial evidence to support the removal of the existing limit of 200 actuations for fluticasone.
- This would positively contribute to the following outcomes:
  - Ensure success and long-term relief from symptoms of allergic rhinitis: multiple spray bottle primary packs up to a six month period would last not only during the acute phase of symptoms (2 weeks), but would also provide additional control on the downgraded dose needed to deliver optimal efficacy and control symptoms of a disease that has been described as a chronic inflammatory condition.

- Availability of a treatment needed not only during seasons but also for those patients that fall into the group of permanent sufferers and demand prompt and efficacious relief.
- Reduced costs related to poor control of the disease: Fewer complications/comorbidities, as well as reduced public-health-related issues that consequently reflect important improvement in quality-of-life for patients.
- Strengthen treatment compliance amongst patients, by ensuring the adequate amount of medication needed is readily available.
- Demonstrates a favourable safety profile regarding a long-term use up to 6 months.
- Brings consistency to the Schedule 2 entry for fluticasone so as to be aligned to the similar entry for mometasone.

- In summary:
  - The benefit:risk profile of the fluticasone is highly favourable.
  - The purpose of the product is for the prevention and treatment of allergic rhinitis. Its clinical benefits in this indication have been established.
  - The global safety experience with fluticasone is extensive and the safety profile is well-defined and not expected to change due to the access changes. There is consistent evidence from clinical trial data and from post-marketing experience that existing non-prescription use results in good tolerability.
  - Extensive post-marketing experience has established that the likelihood of off-label use is extremely low and that abuse or misuse of the fluticasone in this treatment setting is unlikely to be a significant problem.

Current scheduling status

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

Schedule 2

FLUTICASONE in aqueous nasal sprays delivering 50 micrograms or less of fluticasone per actuation when the maximum recommended daily dose is no greater than 400 micrograms and when packed in a primary pack containing 200 actuations or less, for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

Schedule 4

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

Related substances listed in Schedule 2 in the Poisons Standard are as follows:

Schedule 2

BECLOMETASONE in aqueous nasal sprays delivering 50 micrograms or less of beclometasone per actuation when the maximum recommended daily dose is no greater than 400 micrograms and when packed in a primary pack containing 200 actuations or less, for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

BUDESONIDE in aqueous nasal sprays delivering 50 micrograms or less of budesonide per actuation when the maximum recommended daily dose is no greater than 400 micrograms and when packed in a primary pack containing 200 actuations or less, for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

MOMETASONE in aqueous nasal sprays delivering 50 micrograms or less of mometasone per actuation when the maximum recommended daily dose is no greater than 200 micrograms for the prophylaxis or treatment of allergic rhinitis for up to six months in adults and children 12 years of age and over.

TRIAMCINOLONE in aqueous nasal sprays delivering 55 micrograms or less of triamcinolone per actuation when the maximum recommended daily dose is no greater than 220 micrograms, for prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

Scheduling history

In April 1994, the National Drugs and Poisons Scheduling Committee (NDPSC) considered an application for fluticasone propionate for the prophylactic management of asthma in adults and children. The committee decided to include fluticasone in Schedule 4.

In November 2000, the NDPSC considered an application to reschedule fluticasone aqueous nasal spray from Schedule 4 to Schedule 3 for the prophylaxis or treatment of seasonal allergic rhinitis, with an inclusion in Appendix H – Schedule 3 Poisons Permitted to be Advertised. Due to the proposed fluticasone nasal spray formulation being comparable in safety to other Schedule 3 nasal corticosteroids, the committee decided to down-schedule fluticasone from Schedule 4 to Schedule 3, with a maximum daily dose of no greater than 200 micrograms in a primary pack containing 200 actuations or less, for the short-term prophylaxis or treatment of seasonal allergic rhinitis in adults and children 12 years and over.

In November 2001, the NDPSC considered an application to reschedule fluticasone intranasal spray for perennial allergic rhinitis from Schedule 4 to Schedule 3. The committee agreed to amend the Schedule 3 entry for fluticasone to allow a maximum daily dose of no greater than 400 micrograms, in a primary pack containing 200 actuations or less, for up to 6 months in adults and children 12 years and over.

In October 2003, the NDPSC considered an application to reschedule fluticasone from Schedule 3 to Schedule 2 for the short-term (3-6 month) prophylaxis or treatment of allergic rhinitis in adults and children 12 years and over. The committee agreed to include intranasal fluticasone propionate in Schedule 2 with a maximum daily dose of no greater than 400 micrograms in a primary pack containing 200 actuations or less, and removal of fluticasone from Appendix H. The decision was based on the safety of use, low incidence of adverse effects, availability of pharmacist advice or counselling when required, use for a minor ailment that is easily identified, low potential of misuse and abuse and the low potential to mask a serious disease.

In February 2006, the NDPSC considered a recommendation that Australia adopt the New Zealand maximum daily dose limit of 200 micrograms of fluticasone in Schedule 2 due to fluticasone being twice as potent as the other nasal corticosteroids. Members agreed to harmonise with the New Zealand scheduling and amended the Schedule 2 entry to a maximum recommended daily dose of no greater than 200 micrograms.

In February 2007, the NDPSC agreed to an editorial amendment to the Schedule 2 entry of fluticasone to add 'of age' after '12 years'. The Schedule 2 entry still reads as a maximum daily dose of no greater than 400 micrograms.

In June 2008, the NDPSC considered an application for the new medicine fluticasone furoate. The committee agreed that fluticasone furoate is captured under the Schedule 4 and Schedule 2 entries for fluticasone.

Australian regulations

Fluticasone does not appear in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2018, as it is a scheduled ingredient and is not eligible for use in ARTG listed medicines.

The Australian Register of Therapeutic Goods (ARTG) has 80 products listed that contain fluticasone furoate and fluticasone propionate. The products marketed include nasal drops, nasal sprays, metered dose inhalers and accuhalers.

In the last 30 years there have been 809 reported cases of adverse events related to fluticasone in the Database of Adverse Events Notification (DAEN) - Medicines: 640 cases with a single suspected medicine and 8 cases where death was a reported outcome.

According to the TGA Ingredient Database, fluticasone propionate and fluticasone furoate are available for use as an:

- Active Ingredient in: Biologicals, Export Only, Over the Counter (fluticasone propionate only), Prescription Medicines; and
- Excipient Ingredient in: Biologicals, Devices, Prescription Medicines.

International regulations

Canada

Health Canada regulates fluticasone in a nasal spray (50 microgram per spray) as an over-the-counter medicine.

New Zealand

Ingredient	Conditions (if any)	Classification
Fluticasone	**except** when specified elsewhere in this schedule	Prescription
Fluticasone	for the treatment or prophylaxis of allergic rhinitis in adults and children over 12 years of age when in aqueous nasal sprays delivering up to 50 micrograms per actuation with a maximum recommended daily dose of 200 micrograms (as a single dose) in a pack containing 200 actuations or less	Pharmacy Only

United Kingdom (UK)

The UK regulates fluticasone as a:

- Prescription only medicine including creams, ointments, nasal drops, nasal sprays, metered dose inhalers, nebules and accuhalers;
- Pharmacy only medicine including 0.05% nasal spray (fluticasone propionate); and
- General sales list medicine including 0.05% nasal spray (fluticasone propionate).

Substance summary

Fluticasone propionate is the propionate salt form of fluticasone, a synthetic trifluorinated glucocorticoid receptor agonist with anti-allergic, anti-inflammatory and antipruritic effects.

Fluticasone is an extremely potent vasoconstrictor and anti-inflammatory agent. Its effectiveness in inhaled forms is due to its direct local effect. Approved indications for fluticasone via inhalation include COPD, asthma and allergic rhinitis.

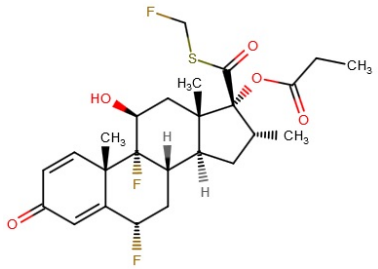
Description: A white to off white crystalline powder.

Solubility: Practically insoluble in water, freely soluble in dimethyl sulfoxide, dimethylformamide and slightly soluble in methanol and 95% ethanol.

Stability: A saturated aqueous solution has a pH of 7.5 to 9.5 and is stable if stored in an airtight container and is protected from light. The stability decreases in acidic conditions, the fluticasone and propionate ion being disassociated from the salt form (fluticasone propionate).

Stability: Stable under normal conditions. Light sensitive in solution/suspension.

Table 1.3A: Chemical information of fluticasone propionate

Property	Fluticasone propionate
CAS number	80474-14-2
Chemical structure	 [as fluticasone propionate]
Molecular formula	$C_{25}H_{31}F_3O_5S$
Molecular weight	500.6 g/mol
IUPAC and/or common and/or other names	*S*-(fluoromethyl)-6α,9-difluoro-11β, 17-dihydroxy-16α-methyl-3-oxoandrosta-1, 4-diene-17β-carbothioate, 17-propanoate (IUPAC); Fluticasone propionate (AAN).

Pre-meeting public submissions

Three (3) public submissions were received, two (2) in support and one (1) conditionally supporting the proposal.

The main points provided in support of the amendment were:

- Fluticasone has been available in Australia for approximately 30 years and the safety and efficacy are well characterised.

- The use of intranasal corticosteroids is recommended for the effective long-term management of the symptoms of allergic rhinitis. Intranasal corticosteroids have a minimal risk of systemic side effects due to their low bioavailability.
- 200 actuations is approximately 1.5-3 month's usage of fluticasone depending on usage. The current Schedule 2 entry allows for up to six months' therapy. Effective long-term management of allergic rhinitis typically involves longer periods of continuous use, and by removing the actuation limit, it has the potential to improve adherence.
- The scheduling proposal will align the Schedule 2 entry for fluticasone with mometasone. It will also be consistent with the scheduling factors for Schedule 2 medicines.

The main points in provided in conditional support of the amendment were:

- It was noted that other corticosteroids for similar indications such as seasonal allergic and perennial rhinitis (i.e. beclometasone and budesonide) have a 200 actuation limit in their Schedule 2 entries in the Poisons Standard.
- Intranasal corticosteroid treatment may require lengthy periods of treatment, including for many years. Given this, the inclusion of an actuation treatment may be unnecessary and be related to the expiry date of the particular formulation after opening.
- If there is no clinical justification for an intranasal corticosteroid entry to have the inclusion of a limit of actuations, then it should be removed. However, if there is clinical justification for an intranasal corticosteroid entry to have the inclusion of a limit of actuations, then it should be included in the entry. As a result, it was recommended that all intranasal corticosteroid Schedule 2 entries be reconsidered.

The public submissions will be made available on the TGA website.

Summary of ACMS advice to the delegate

The committee recommended the Schedule 2 entry for fluticasone be amended in the Poisons Standard as follows:

> **Schedule 2 – Amend Entry**
>
> FLUTICASONE in aqueous nasal sprays delivering 50 micrograms or less of fluticasone per actuation when the maximum recommended daily dose is no greater than 400 micrograms ~~and when packed in a primary pack containing 200 actuations or less,~~ for the prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

The committee also recommended an implementation date of **1 October 2018**.

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

The reasons for the advice included:

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

- Benefits:
  - Over 30 years' experience with this agent in Australia including 16 years non-prescription experience.
  - Intranasal corticosteroids such as fluticasone are well-established as recommended agents for effective long-term management of symptoms of allergic rhinitis with favourable long-term use safety profile.
  - Long-term safety profile established from clinical trials and extensive post-marketing data with insignificant systemic absorption of fluticasone from intranasal administration or any portion of dose that is swallowed.
- Making the agent available in a larger pack size is unlikely to impact the risk:benefit profile significantly.

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

- Symptomatic treatment and prophylaxis of allergic rhinitis in adults and children over 12 years.
- Australian prevalence of allergic rhinitis ranges from 12-26% (AIHW analysis of ABS National Health Survey, 2014–15).

c) the toxicity of a substance:

- High tolerability and safety with low frequencies of adverse events reported in clinical trials and post-marketing.

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

- Removal of actuation limit would allow the supply of a larger number of doses per occasion of supply to treat a chronic condition, providing up to 6-months of treatment, which will enhance adherence, improve symptom control and quality of life, and reduce medicine and healthcare resource costs.

e) the potential for abuse of a substance:

- Nil.

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

- Minimising barriers to compliance with intranasal corticosteroids is of benefit.
- Enhanced consumer access and treatment continuity.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACMS advice;
- Public submissions received;

- Scheduling Policy Framework (SPF 2018); and
- Section 52E (1) of the *Therapeutic Goods Act 1989*, in particular: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

2. Joint meeting of the Advisory Committee on Chemicals and Medicines Scheduling (ACCS/ACMS #18)

2.1 Prostaglandins

Delegate's interim decision

The delegate's interim decision is that the current scheduling of all prostaglandins in the Poisons Standard remains appropriate.

Reasons:

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

- Each substance was considered on its own risks and pattern of use
- Risk: Including all prostaglandins for obstetrics/gynaecology use in Appendix D Item 1 would restrict prescribing this class of substance to authorised medical practitioners. Doctors who may require to use them in an emergency would not be able to access them.

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

- Multiple therapeutic uses exist for prostaglandins as there are multiple compounds.
- In the context of this agenda item, prostaglandins are used for:
  - The treatment of post-partum haemorrhage due to uterine atony;
  - For the therapeutic termination of pregnancy; and
  - For induction of labour.

c) the toxicity of a substance:

- Variable depending on prostaglandin however not relevant to putting increased controls on all of them.

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

- Variable depending on prostaglandin however not relevant to putting increased controls on all of them.

e) the potential for abuse of a substance:

- Limited.

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

- Including all prostaglandins for obstetrics/gynaecology use in Appendix D Item 1 would restrict prescribing this whole class of substance to authorised medical

practitioners. Doctors who may require to use them in an emergency would not be able to access them.

– It is appropriate that the current prostaglandins in Appendix D remain there.

Scheduling proposal

The pre-meeting scheduling proposal for prostaglandins was published on the TGA website on 21 December 2017 at Consultation: Proposed Amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS-ACMS meetings, March 2018.

Background information for prostaglandins

Referred scheduling proposal

The delegate of the Secretary proposed an amendment to the scheduling of prostaglandins in the Poisons Standard by either:

- Placing all applicable prostaglandins in Appendix D Item 1 and include a general entry in Appendix D Item 1 for 'PROSTAGLANDINS when used in obstetrics/gynaecology';

  OR

- Removing those prostaglandins currently listed in Appendix D Item 1

Scheduling application

The proposed amendments to the Poisons Standard are reflected below:

Appendix D, Item 1 – New Entries

CARBOPROST for obstetrics/gynaecology use.

CLOPROSTENOL for obstetrics/gynaecology use.

ETIPROSTON for obstetrics/gynaecology use.

FENPROSTALENE for obstetrics/gynaecology use.

FLUPROSTENOL for obstetrics/gynaecology use.

GEMEPROST for obstetrics/gynaecology use.

MISOPROSTOL for obstetrics/gynaecology use.

PROSTIANOL for obstetrics/gynaecology use.

Appendix D, Item 1 – Amend Entries

DINOPROST for obstetrics/gynaecology use.

DINOPROSTONE for obstetrics/gynaecology use.

PROSTAGLANDINS for obstetrics/gynaecology use.

The reasons for the proposal are:

- Inconsistencies in prostaglandin entries in Schedule 4 and Appendix D Item 1.

Current scheduling status

Prostaglandins are listed in Schedule 4 of the Poisons Standard as follows:

Schedule 4

ALPROSTADIL.

BIMATOPROST.

CARBOPROST.

CLOPROSTENOL.

DINOPROST.

DINOPROSTONE.

ENPROSTIL.

EPOPROSTENOL.

ETIPROSTON.

FENPROSTALENE.

FLUPROSTENOL.

GEMEPROST.

ILOPROST.

LATANOPROST.

MISOPROSTOL.

PROSTAGLANDINS.

PROSTIANOL.

TAFLUPROST.

TRAVOPROST.

TREPROSTINIL.

UNOPROSTONE.

Some are also included in Appendices D, F and L as follows:

Appendix D, Item 1

DINOPROST for human use.

DINOPROSTONE for human use.

Appendix F, Part 3

MISOPROSTOL

Appendix L, Part 2

MISOPROSTOL.

Scheduling history

Prostaglandins

In August 1975, the Poisons Schedule Sub-Committee (PSSC) considered a previous deferred item to include prostaglandins in Schedule 7 due to concerns of use in cattle and sheep and whether an entry should be made to cover research work. The PSSC agreed that prostaglandins should be included in Schedule 7 as they are new substances, have a wide range of biological activities and their functions are not fully understood. The PSSC also recommended only allowing availability to medical practitioners and veterinary surgeons with a specialised knowledge and experience with these types of substances, and only for approved research purposes.

In May 1981, the Poisons Schedule Committee (PSC) noted that the Schedule 7 entry for prostaglandins may not be appropriate, and they should be rescheduled from Schedule 7 to Schedule 4. This was deferred to the next meeting.

In November 1981, after agreeing to the inclusion of fenprostalene in Schedule 4 for animal use, the PSC agreed to amend the Schedule 7 entry for prostaglandins to include the words 'except when included in Schedule 4'.

In February 1982, the PSC discussed concerns raised by State and Territories in regards to the difficulties encountered with the Schedule 7 entry of prostaglandins being only for human use. It was agreed that they should continue being handled by State and Territories through appropriate amendments to regulations, rather than amending the Poisons Standard (SUSMP).

In November 1982, the PSC considered a letter regarding the scheduling of prostaglandins proposing that these therapeutic drugs require additional controls on possession and supply applied to them. It was recommended that a Schedule 4 and Appendix D listing would be more appropriate than their existing Schedule 7 entry. The committee agreed to the recommendation and deleted its Schedule 7 entry and created new entries in Schedule 4 and Appendix D with the control 'these substances should be available only to medical practitioners and veterinary surgeons with a specialised knowledge and experience with these types of substances, and for approved research purposes'.

In February 1985, the PSC discussed a recommendation to increase restrictions on the availability of prostaglandins due to an adverse reaction. The committee agreed that the current scheduling remained appropriate. The committee agreed that Appendix D was to be amended and split into two parts, and prostaglandins added to Appendix D, Part 1 – 'drugs to be available only from or on prescription of person or classes of person specifically authorised'.

In August 1986, the Drugs and Poisons Schedule Committee (DPSC) considered the issue of including specific prostaglandin entries in Schedule 4 and amending the Appendix D rider. This was due to a new prostaglandin product indicated to treat gastric or duodenal ulcers, but contraindicated for use in pregnancy and restricted for use by the Appendix D 'prostaglandins' class entry for specialist prescriptions. The matter was deferred to November 1986.

In November 1986, the DPSC reviewed the issue raised in the previous meeting. It was agreed that prostaglandin preparations for routine therapy should be available in Schedule 4, whereas the more specialised use products, (obstetrics, gynaecology, endocrinology) should be confined to specialist use. In situations where no specialist was available (rural areas etc.), medical practitioners authorised by State/Territory Health authorities would be permitted to use them. The committee agreed to individual entries in Appendix D, although the class entry for prostaglandins would be retained in Schedule 4, but deleted from Appendix D. It was also agreed to delete 'for treatment of animals' from existing individual prostaglandin entries in Schedule 4 as there was no need to refer to veterinary specialists.

In February 1993, the DPSC noted that no rationale had been stated to place dinoprostone in Appendix D. It was agreed that a rationalisation of the class of prostaglandins needed to be considered by the committee at a future meeting.

Alprostadil

In May 1982, the PSC agreed that alprostadil was already covered by the general Schedule 7 entry for prostaglandins.

In November 1986, the DPSC agreed to include alprostadil in Schedule 4.

In November 1997, the National Drugs and Poisons Scheduling Committee (NDPSC) considered an inclusion of alprostadil in Appendix D to prevent misuse. The committee decided to defer the decision as more information was required.

Bimatoprost

In October 2002, the NDPSC considered the scheduling of bimatoprost. The committee agreed to include bimatoprost in Schedule 4 on the grounds that the condition being treated required professional diagnosis, management and monitoring of the indicated condition and any side effects.

Carboprost

In November 1998, the NDPSC agreed to create a new Schedule 4 entry for carboprost due to consolidation of scheduling proposals arising from the Trans-Tasman Harmonisation of Scheduling of Drugs and Poisons Working Party.

Cloprostenol

In November 1975, the PSSC considered an application for the scheduling of cloprostenol. The sub-committee recommended a new Schedule 4 entry be created for the treatment of animals, and to amend the Schedule 7 entry for prostaglandins to exempt cloprostenol when included in Schedule 4.

In February 1982, the PSC discussed concerns raised by state and territories in regards to the difficulties encountered around prostaglandins. The subcommittee agreed to keep cloprostenol in Schedule 4 entry for the treatment of animals.

In November 1986, the DPSC agreed to delete from the Schedule 4 entry of cloprostenol the words 'for the treatment of animals'.

Dinoprost

In February 1982, the PSC agreed to create a new Schedule 4 entry for dinoprost for the treatment of animals.

In November 1986, the DPSC agreed to amend the Schedule 4 entry for dinoprost by deleting the words 'for the treatment of animals' and to also include dinoprost in Appendix D with the wording 'for human use' and 'this substance should be available only on the prescription or order of authorised medical practitioners.

In August 1997, the NDPSC considered a submission to remove dinoprost and dinoprostone from Appendix D which restricts its prescribing. The discussion was deferred to allow states and territories time to consult with jurisdictions and legislation.

In November 1997, the NDPSC agreed that dinoprost and dinoprostone should not be removed from Appendix D due to state and territory regulations.

Dinoprostone

In February 1991, the DPSC agreed to include dinoprostone in Schedule 4 and Appendix D for human use.

In February 1993, the DPSC noted that no rationale had been stated to place dinoprostone in Appendix D and how confusion has arisen as to why it is more difficult to obtain than gemeprost and other prostaglandins in Schedule 4. It was noted that general practitioners (GPs) do not support the Appendix D inclusion. It was agreed that this needed to be considered at a future meeting.

In August 1997, the National Drugs and Poisons Scheduling Committee (NDPSC) considered a submission to remove dinoprost and dinoprostone from Appendix D which restricts its prescribing. The discussion was deferred to allow States and Territories time to consult with jurisdictions and legislation.

In November 1997, the NDPSC agreed that dinoprost and dinoprostone should not be removed from Appendix D due to State and Territory regulations.

Enprostil

In November 1998, the NDPSC agreed to create a new Schedule 4 entry for enprostil due to consolidation of scheduling proposals arising from the Trans-Tasman Harmonisation of Scheduling of Drugs and Poisons Working Party.

Epoprostenol

In November 1999, the NDPSC agreed to include epoprostenol in Schedule 4 to harmonise with the Prescription Medicine classification in New Zealand.

Etiproston

In May 1996, the NDPSC considered an application for etiproston as a veterinary injectable. The committee noted that etiproston was covered by the class Schedule 4 entry for prostaglandins, but agreed that for clarification a separate Schedule 4 entry for etiproston was appropriate.

Fenprostalene

In November 1981, the PSC considered an application for fenprostalene, a synthetic analogue of the naturally occurring prostaglandin PGF2 alpha, to create a new entry in Schedule 4, even though the group entry for prostaglandins is in Schedule 7. The committee agreed that fenprostalene is well classified in Schedule 4 for animal use.

In November 1986, the DPSC agreed to delete from entry the words ‘for the treatment of animals’.

Fluprostenol

In February 1982, the PSC agreed to create a new Schedule 4 entry for fluprostenol for the treatment of animals.

In November 1986, the DPSC agreed to delete from the Schedule 4 entry of fluprostenol the words ‘for the treatment of animals’.

Gemeprost

In November 1986, the DPSC was advised that general practitioners should have access to gemeprost as it has a place in routine dilation and curettage (D & C) procedures. A new Schedule 4 entry was created.

In February 1991, the DPSC considered correspondence to include gemeprost in Appendix D, restricting its use to specialised physicians and/or institutions due to the potential for misuse. The members agreed that more research is required to investigate if gemeprost is being misused and to report back to a future meeting.

In November 1997, the NDPSC again considered an inclusion of gemeprost in Appendix D. The committee noted that this would achieve consistency among the group and was important due to the possible use of gemeprost by GPs to induce abortion. The committee noted that gemeprost was also indicated for surgical purposes, and placing gemeprost in Appendix D may remove access by GPs. The committee decided to defer the decision as more information was required.

In November 1998, the NDPSC revisited the consideration to include gemeprost in Appendix D. The committee agreed that inclusion of gemeprost in Appendix D would disadvantage certain States and Territories due to various mechanisms placed on Appendix D. The committee did not support the inclusion of gemeprost in Appendix D.

Iloprost

In November 1998, the NDPSC agreed to create a new Schedule 4 entry for iloprost due to consolidation of scheduling proposals arising from the Trans-Tasman Harmonisation of Scheduling of Drugs and Poisons Working Party.

Latanoprost

In May 1997, the NDPSC considered an application for a latanoprost eye drop was submitted and agreed to include latanoprost in Schedule 4.

Misoprostol

In May 1986, the DPSC agreed to include misoprostol in Schedule 4 after the Australian Drug Evaluation Committee (ADEC) had recommended approval of a product containing misoprostol.

In November 1986, the DPSC noted the warning statement for misoprostol regarding pregnant women in a handbook, and agreed to liaise with the sponsor and regulators regarding suitable warning labels.

In February 1990, the DPSC considered the need for misoprostol to be labelled with a warning statement for pregnant women. The committee agreed to include misoprostol in Appendix F, Part 2 with a new Warning Statement 53 '*CAUTION (name of substance) should not be used by pregnant women)'*.

In October 2007, the NDPSC considered an issue raised of inconsistencies between listings in Appendix D and ADEC's 'Prescribing Medicines in Pregnancy' handbook. It was noted that misoprostol is listed in ADEC's Category X but is not in Appendix D. The committee decided that misoprostol did not warrant inclusion in Appendix D as the original packaging requires a label warning statement due to its inclusion in Appendix F Part 3.

Prostianol

In February 1982, the PSC agreed to create a new Schedule 4 entry for prostianol for the treatment of animals.

In November 1986, the DPSC agreed to delete from entry the words 'for the treatment of animals'.

Tafluprost

In December 2010, the delegate considered an application to register tafluprost eye drops and decided that a Schedule 4 entry was appropriate. The delegate noted reproductive toxicity data and raised concerns during pregnancy and decided to refer it to the Advisory Committee on Medicines Scheduling (ACMS).

In February 2011, the ACMS considered a proposal to include tafluprost in Appendices D and L. The committee recommended that the scheduling of tafluprost remain unchanged (i.e. in Schedule 4 with no new Appendix D or L entry).

Travoprost

In June 2002, the NDPSC considered the scheduling of travoprost. The committee agreed to include travoprost in Schedule 4 on the grounds that the condition being treated required diagnosis and management by a medical professional.

Treprostinil

In June 2004, the NDPSC considered the scheduling of treprostinil. The committee agreed to include treprostinil in Schedule 4 on the grounds that the condition being treated necessitated appropriate medical diagnosis and the safe use of this medicine required administration, ongoing patient management and monitoring by a medical professional.

Unoprostone

In November 2000, the NDPSC considered a request to include unoprostone in Schedule 4 to harmonise with NZ. The committee agreed to create a Schedule 4 entry for unoprostone as it is a new substance that treats a condition that requires medical management and on the grounds of harmonisation.

Australian regulatory information

The Australian Register of Therapeutic Goods (ARTG) has 82 registered products with prostaglandins:

- Alprostadil – 5 registered products for injection as powder preparations or solutions for erectile dysfunction;
- Bimatoprost – 11 registered products as solutions for eye drops;
- Dinoprost – 3 registered products for injection as solution preparations for pregnancy termination;
- Dinoprostone – 4 registered products as gel preparations for labour induction;
- Epoprostenol – 8 registered products for injection as powder preparations or solutions for pulmonary hypertension;
- Gemeprost – 1 registered product as gel preparation for pregnancy termination;
- Iloprost – 1 registered product in nebuliser solution for pulmonary hypertension;
- Latanoprost – 36 registered products as solutions for eye drops;

- Misoprostol – 7 registered products in tablet form for gastrointestinal ulceration and/or bleeding;
- Tafluprost – 1 registered product as a solution for eye drops; and
- Travoprost – 5 registered products as a solution for eye drops.
- Currently no registered products listed on the ARTG for the following prostaglandins: carboprost, cloprostenol, enprostil, etiproston, fenprostalene, fluprostenol, prostianol, treprostinil and unoprostone.

There is no reference to prostaglandins in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2018, as they are scheduled substances and are not eligible for use in ARTG listed medicines.

The APVMA PubCRIS database has 14 registered and 4 approved products with prostaglandins.

- Cloprostenol – 10 registered and 4 approved products in parenteral liquid / solution, for the regulation of bovine, equine and porcine oestrus cycles or farrowing.
- Dinoprost – 3 registered products in parenteral liquid / solution, for the regulation of bovine, equine and porcine oestrus cycles, abortion or parturition.
- Etiproston – 1 registered products in parenteral liquid / solution, for the regulation of bovine oestrus cycles, abortion or parturition or the treatment of endometritis.

In the last 30 years there have been 1,962 reported cases of adverse events related to prostaglandins in the Database of Adverse Events Notification (DAEN) - Medicines: Of the 21 listed prostaglandins, a total of 870 cases with a single suspected medicine have been reported and 33 cases where death was a reported outcome.

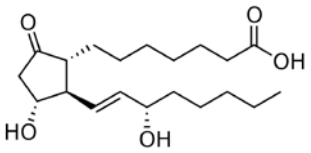
International regulations

- Alprostadil – New Zealand (NZ): Prescription; and the United States of America (USA): Prescription.
- Bimatoprost – Canada: Prescription and USA: Prescription.
- Carboprost – USA: Prescription.
- Cloprostenol – Canada: Prescription.
- Dinoprost – European Union (EU): Annex II, No 2377/90 and USA: discontinued.
- Dinoprostone – Canada: Prescription, EU: Annex II, No 2377/90 and USA: Prescription.
- Epoprostenol – Canada: Prescription and USA: Prescription.
- Etiproston – EU: Annex II, bovine, porcine.
- Fenprostalene – EU: withdrawn.
- Fluprostenol – Canada: Prescription.
- Iloprost – NZ: Prescription and USA: Prescription.
- Latanoprost – NZ: Prescription, Canada: Prescription, EU: Prescription and USA: Prescription.
- Misoprostol – NZ: Prescription, EU: Prescription and USA: Prescription.

- Tafluprost – NZ: Prescription, EU: Prescription and USA: Prescription.
- Travoprost – NZ: Prescription, EU: Prescription and USA: Prescription.
- Treprostinil – Canada: Prescription, EU: Prescription and USA: Prescription.
- Unoprostone – Canada: Prescription and USA: Prescription.

Substance summary

Table 2.1A: Chemical information for prostaglandins

Property	Prostaglandins
CAS name	Multiple
CAS number	Multiple
Chemical structure	
Molecular formula	Multiple
Molecular weight	Multiple
IUPAC and/or common and/or other names	Multiple

Prostaglandins are a diverse family of lipid compounds derived from arachidonic acid via the action of cyclooxygenase enzymes (COX). They have hormone-like effects that maintain homeostatic functions and have pathogenic and inflammatory actions.

The physiological actions of prostaglandins vary from one tissue to another and can determine blood vessel diameter (vasodilators or vasoconstrictors), have roles in thrombosis (pro- or anti-clot formation), pain sensitisation, parturition, gastric mucous production and bicarbonate secretion, calcium movement and renal filtration, among many other functions.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) is a common means of reducing the production of prostaglandins via the inhibition of COX enzymes.

Pre-meeting public submissions

One (1) public submission was received in support of the proposal.

The main point provided in support of the amendment was:

- The public submission endorsed the option of placing all applicable prostaglandins in Appendix D, Item 1 in the Poisons Standard and to include a general entry in Appendix D, Item 1 for '*PROSTAGLANDINS for obstetrics/gynaecology use*'. This will increase uniformity and help manage medication safety.

The public submission will be made available on the TGA website.

Summary of ACCS-ACMS advice to the delegate

The committee recommended that the current scheduling of all prostaglandins remains appropriate.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse of a substance.

The reasons for the advice were:

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

- Each substance was considered on its own risks and pattern of use
- Risk: Including all prostaglandins for obstetrics/gynaecology use in Appendix D Item 1 would restrict prescribing this class of substance to authorised medical practitioners. People who may require these in an emergency cannot access them.

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

- Multiple therapeutic uses exist for prostaglandins as there are multiple compounds.
- There are a variety of therapeutic uses for prostaglandins.
- In the context of this agenda item, prostaglandins are used for:
  - The treatment of post-partum haemorrhage due to uterine atony;
  - For the therapeutic termination of pregnancy; and
  - For induction of labour.

c) the toxicity of a substance:

- Variable.

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

- Variable.

e) the potential for abuse of a substance:

- Limited.

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

- Nil.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS-ACMS advice;
- Public submission received;

- Scheduling Policy Framework (SPF 2018); and
- Section 52E (1) of the *Therapeutic Goods Act 1989*, in particular: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

2.2 Vinyl Acetate

Delegate's interim decision

The delegate's interim decision is to amend the Schedule 6 entry for vinyl acetate in the Poisons Standard as follows:

Schedule 6 – Amend Entry

VINYL ACETATE MONOMER (excluding its derivatives) **except**:

a) in preparations for therapeutic use; or

b) in cosmetic preparations containing 0.01 per cent or less of vinyl acetate as residual monomer in a polymer; or

c) in other preparations containing 1 per cent or less of vinyl acetate.

Proposed implementation date: 1 October 2018

The delegate considers the Committee's proposed implementation date of 1 October 2018 (to replace the 31 October 2017 decision) as being reasonable and appropriate in the circumstances.

Reasons:

The delegate has decided to retain the words *'as residual monomer in a polymer'* and 'MONOMER' in the Schedule 6 entry for vinyl acetate to ensure that the intention of the schedule entry – to capture only monomer vinyl acetate and not polymer vinyl acetate – is clear for all stakeholders.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

- Risks arise from evidence of carcinogenicity and mutagenicity. Although the evidence is limited, there is enough evidence to consider risk mitigation.
- Vinyl acetate is a monomer that is useful in a number of domestic formulations that require liquid consistency which polymerises or 'sets' to give a solid finish e.g. paints, sealants, adhesives, etc. It is not expected to be a simple matter to replace this technology.
- There is a risk that non-cosmetic and non-therapeutic products will be captured inappropriately.
- Highly flammable.
- Respiratory and carcinogenicity health effects on humans.
- Domestic use has potential for general public to be exposed via vapour inhalation or dermal contact.
- Use of chemical in cosmetics banned in Europe from 2015.

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

- Vinyl acetate is used in paints, lacquers, varnishes, adhesives, sealants.
- Vinyl acetate is also a starting raw material in polymer production.
- Vinyl acetate may be present as an impurity in a wide range of products containing vinyl acetate polymers and copolymers, including in domestic products, cosmetics and therapeutic goods.
- Domestic use - widespread in the general population.
- Commercial/Industrial use - building, textile and paper.
- Confined space/inappropriate use and storage and skin contact.
- Potential variations or non-adherence to use and storage by general public.
- Possible cosmetic application to skin - Vinyl Acetate use in cosmetics in Australia not known, but may potentially be present in some nail varnish preparations.

c) the toxicity of a substance:

- Potential carcinogen, based on limited evidence of carcinogenicity in experimental animals.
- Potential mutagen (limited evidence), which may be due to formation of acetaldehyde (hydrolysis under aqueous conditions).
- Respiratory irritancy, genotoxic potential at high doses and carcinogenic potential

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

- Can vary depending on product type and use for domestic products and in industrial manufacturing.
- Packaging and presentation as per current proposed scheduling.

Scheduling proposal

The pre-meeting scheduling proposal for vinyl acetate was published on the TGA website on 21 December 2017 at Consultation: Proposed Amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS-ACMS meetings, March 2018.

Background information for vinyl acetate

Referred scheduling proposal

An application was submitted to amend the Poisons Standard with respect to vinyl acetate. The application proposes to amend the Schedule 6 entry for vinyl acetate.

Scheduling application

The proposed amendments to the Poisons Standard are:

Schedule 6 – Amend Entry

VINYL ACETATE

a) in preparations for therapeutic use; or

b) in preparations for domestic use containing 1 per cent or less of vinyl acetate; or

c) in preparations containing 0.01 per cent or less of vinyl acetate as residual monomer in a polymer used in direct contact with the body, such as cosmetic preparations.

The applicant's reasons for the proposal are:

- The Inventory Multi-tiered Assessment and Prioritisation (IMAP) and scheduling documentation for the Schedule 6 entry for vinyl acetate for domestic use of 'with 0.01% or less of residual vinyl acetate monomer' to be implemented 1 October 2018 indicates that the scheduling is meant to be for polymers used in direct contact with the body (such as cosmetic preparations).
- The chosen wording captures 'Do It Yourself' (DIY) type products containing polymers with trace residual vinyl acetate monomer >0.01% (e.g. paints).
- The applicant ensures all its copolymer raw materials have <0.10% vinyl acetate, in line with Globally Harmonised System (GHS) hazard classification criteria to be not hazardous chemicals.
- However, as the applicant's polymer products have trace residual vinyl acetate monomer in the range of 0.011 to 0.099% (~0.01%), many of these polymer containing products would become Schedule 6 Poisons when formulated into domestic DIY products.
- None of these DIY products are intended for body contact applications.
- The proposed change to the wording makes it clear that these types of products, which will not be used in direct contact with the body, are not scheduled.
- Then exception (b) of the Schedule 6 entry of vinyl acetate would be applied for vinyl acetate in preparations for domestic use containing 1% or less of vinyl acetate.

Current scheduling status

Vinyl acetate is unscheduled but is due to be included in Schedule 6 of the Poisons Standard October 2018 as follows:

Schedule 6

VINYL ACETATE MONOMER (excluding its derivatives) **except:**

a) in preparations for therapeutic use; or

b) in preparations for domestic use containing 1 per cent or less of vinyl acetate; or

c) in preparations containing 0.01 per cent or less of vinyl acetate as residual monomer in a polymer.

Appendix E, Part 2

VINYL ACETATE

Standard Statements: A (For advice, contact a Poisons Information Centre or a doctor); R1 (If inhaled, removed from contaminated area. Apply artificial respiration if not breathing).

Appendix F, Part 3

VINYL ACETATE

Warning Statement: 11 (Vapour may be harmful).

Safety Directions: 8 (Avoid breathing vapour); 9 (Use only in well ventilated area).

Scheduling history

In July 2017, the Joint Advisory Committee on Chemicals and Medicines Scheduling (ACCS-ACMS) considered an application to include vinyl acetate in Schedule 6 of the Poisons Standard with a cut-off of 1% of less in domestic products. The Joint ACCS-ACMS also considered a Schedule 10 entry for use in cosmetic products, and Appendix E and F entries. The main toxicological concerns discussed were respiratory irritancy, genotoxic potential at high doses and carcinogenic potential. Vinyl acetate was noted to be useful in a number of domestic formulations, with a lack of evidence for cosmetic use in Australia. A Schedule 10 listing was not considered necessary. The delegate made a final decision to include vinyl acetate in Schedule 6 with exceptions for therapeutic use, preparations for domestic use containing 1% or less of vinyl acetate and preparations containing 0.01% or less as residual monomer in a polymer, along with Appendix E and F entries. The implementation is 1 October 2018.

Australian regulations

Vinyl acetate is not in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2018 but is listed in the previous determination (No. 5 of 2017) as follows:

Column 1	**Column 2** **Ingredient Name**	**Column 3** **Purpose of the ingredient in the medicine**	**Column 4** **Specific requirements(s) applying to the ingredient in Column 2**
5042	VA/BUTYL MALEATE/ISOBORNYL ACRYLATE COPOLYMER	E	Vinyl acetate is a mandatory component of VA/butyl maleate/isobornyl acrylate copolymer. The concentration of vinyl acetate in the medicine must be no more than 0.01% or 100 ppm. Only for use in topical medicines for dermal application and not to be included in medicines intended for use in the eye. The concentration in the medicine must be no more than 5%.

According to the TGA Ingredient Database, vinyl acetate is available for use as an:

- Excipient only in biologicals, devices and prescription medicines; and
- Equivalent ingredient in devices, listed medicines and prescription medicines.

Vinyl acetate is in 86 products listed on the Australian Register of Therapeutic Goods (ARTG) including a medical device (Class IIa), non-prescription medicines and prescription medicines.

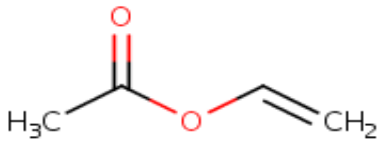
Vinyl acetate is not listed in the Database of Adverse Events Notification (DAEN) - Medicines.

International regulations

- **European Union (EU):** Vinyl acetate is classed as Carcinogenic, Mutagenic, or toxic for Reproduction 2 (CMR 2) (carc.2) substance and is prohibited for use in cosmetics and personal care products in the EU from 1 January 2015, as per EU Regulation No 944/2013.
- **United States of America:**
  - The Food and Drug Administration has determined that vinyl acetate may be safely used as a coating or a part of a coating (e.g. an adhesive) that is used in plastic films for food packaging, and as a modifier of food starch.[14,15]
  - The American Conference of Governmental Industrial Hygienists has established an exposure limit of 10 parts of vinyl acetate per million parts of workplace air (10 ppm) for an 8-hour workday, 40-hour work week.
  - The National Institute for Occupational Safety and Health recommends that exposure to vinyl acetate in the workplace not exceed 4 ppm over a 15-minute period.

Substance summary

Table 2.2A: Chemical information for vinyl acetate

Property	Substance
CAS number	108-05-4
CAS name	acetic acid ethenyl ester
Chemical structure	
Molecular formula	$C_4H_6O_2$

[14] ToxFAQsTM for Vinyl Acetate

[15] Electronic Code of Federal Regulations, Part 175-Indirect Food Additives: Adhesives and Components of Coatings.

Property	Substance
Molecular weight	86.1 g/mol
IUPAC and/or common and/or other names	Ethenyl acetate (IUPAC); Vinyl acetate (INCI, AAN).

Table 2.2B: Acute toxicity end-points for vinyl acetate

Toxicity	Species	Vinyl acetate	SPF (2018) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	2500-3500	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	Rabbit	2335	Schedule 5
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	4490 ppm or ~15810 mg/m^3 (vapour)	Schedule 5
Skin irritation	Rabbit	Slight	Schedule 5
Eye irritation	Rabbit	Slight	Schedule 5
Skin sensitisation (LLNA)	Mouse	Negative	N/A

Acute toxicity

Vinyl acetate has low acute oral and dermal toxicity in animals (LD_{50} >2000 mg/kg bw).

Based on the available data, vinyl acetate (as a vapour) has moderate acute inhalation toxicity in rats.

Irritation

Vinyl acetate has been classified by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) as a respiratory irritant based on effects observed in humans following exposure to vinyl acetate, necropsy findings from acute inhalation studies in animals and clinical signs of toxicity observed in repeat dose inhalation studies in animals.

In male Sprague Dawley (SD) rats exposed (whole body) to vinyl acetate vapour on either one, five or 20 occasions (for six hours per day, five days per week) at concentrations of 50, 200, 600 or 1000 ppm, dose related increase in the severity of microscopic lesions in the olfactory epithelium was observed at 600 ppm and above. Following a single exposure, degeneration, necrosis and exfoliation of olfactory epithelial cells were observed (REACH).

In three-month inhalation studies conducted in rats and mice, clinical signs of toxicity included intermittent symptoms of respiratory distress, hunched posture and ruffled fur in animals exposed to vinyl acetate at 200 – 1000 ppm concentrations. Increased lung weight observed in

rats and mice exposed to vinyl acetate at 1000 ppm was attributed to lung congestion arising from respiratory irritation. Treatment-related lesions were observed at necropsy in the lungs, trachea and nasal epithelium of mice exposed to vinyl acetate at 1000 ppm (REACH).

Vinyl acetate may cause slight eye and skin irritation.

Sensitisation

Based on the negative results observed for vinyl acetate in a well conducted (OECD TG 429 compliant) local lymph node assay (LLNA) in CBA/CaOlaHsd mice, vinyl acetate is not considered to be a skin sensitiser.

Repeat-dose toxicity

Vinyl acetate is not considered to cause severe effects following repeated oral exposure. No data are available on repeated dermal exposure.

Repeated inhalation exposure to vinyl acetate may cause symptoms consistent with respiratory irritation and inflammation. Based on the available data, vinyl acetate is not considered to cause severe systemic effects following repeated inhalation exposure, apart from causing histopathological changes in the olfactory epithelium and respiratory system, which are considered possible evidence of precursor events to tumour formation (see Carcinogenicity).

Genotoxicity

Vinyl acetate showed positive results for genotoxicity, both *in vitro* and *in vivo*. Vinyl acetate undergoes hydrolysis to form acetaldehyde and acetic acid. Acetaldehyde is also a Category 3 mutagen. It has been hypothesised that the genotoxicity of vinyl acetate may be attributable to the formation of acetaldehyde, although the lowering of cell pH that occurs when large doses of vinyl acetate are metabolised to acetic acid may also be a contributing factor (Albertini, 2013).

Vinyl acetate vapour or liquid tested negative for mutagenicity in *Salmonella typhimurium* strains TA 98, 100, 1535, 1537 and 1538, in the presence or absence of metabolic activation (ACGIH, 2001).

Although *in vitro* assays utilising bacterial cells have shown negative results for mutagenicity, positive results have been obtained using mammalian cells (*in vitro* and *in vivo*), particularly for chromosome effects (ACGIH, 2001; IARC, 1995; Norppa *et al*., 1985; REACH).

A dose-dependent and statistically significant increase in sister chromatid exchange (SCE) was observed in human lymphocytes (whole blood culture) following exposure for 48 hours to concentrations of 0.1 mM of vinyl acetate and above. A dose-dependent increase in chromosome aberrations was also observed. An increased number of aberrant cells (gaps included or excluded), number of cells carrying chromatid-type aberrations or chromatid-type exchanges was statistically significant at 0.5 mM (Norppa *et al.*, 1985).

A dose-dependent increase in SCE was observed in Chinese hamster ovary (CHO) cells following exposure to vinyl acetate for 24 hours at doses of 0.125-1 mM or exposure to vinyl acetate for four hours at doses of 0.3-5 mM (Norppa *et al.*, 1985).

Vinyl acetate induced DNA cross links in isolated human lymphocytes and rat nasal epithelial cells at 860 µg/mL (IARC, 1995).

Increased numbers of micronuclei were formed in human lymphoblastoid cells (TK6) following a 4-hour exposure to vinyl acetate concentrations of 0.25, 0.5, 1 or 2 mM in a micronucleus assay (a similar protocol to OECD TG 487). Acetaldehyde, a metabolite of vinyl acetate, was also found to be positive in this same assay at concentrations of 0.25, 0.5 and 1 mM (REACH).

Increased chromosome aberrations were observed in human whole blood and isolated human lymphocytes after exposure (similar to OECD TG 473) to vinyl acetate concentrations of 0.25, 0.5, 1 or 2 mM for 24 hours, without metabolic activation (REACH).

There was an increased frequency of chromosomal aberrations in cultured lymphocytes of humans following occupational exposure (IARC, 1995). No additional details were available.

A dose-dependent increase in micronuclei was observed in C57BL mice that received an intraperitoneal injection of vinyl acetate at 250, 500, 1000 or 2000 mg/kg bw (similar to OECD TG 474). Increases were statistically significant at the two high doses, which caused increased mortality.

Based on the weight of evidence from the available genotoxicity data, vinyl acetate may have genotoxic potential. NICNAS classified vinyl acetate as a Category 3 Mutagen according to the Approved criteria for Classifying Hazardous Substances.

Carcinogenicity

According to the International Agency for Research on Cancer (IARC), vinyl acetate is a Group 2B carcinogen (possibly carcinogenic to humans; IARC, 1995). The IARC classification was based on limited evidence in experimental animals, although the evidence in humans was considered to be insufficient to establish carcinogenicity (IARC, 1995). Vinyl acetate has a harmonised GHS classification in the EU as a Category 2 carcinogen (suspected of causing cancer).

Based on the positive carcinogenicity findings in animals following both oral and inhalational exposure to vinyl acetate, NICNAS classified vinyl acetate as a Category 3 carcinogen according to the Approved Criteria for Classifying Hazardous Substances.

Evidence of vinyl acetate carcinogenicity was obtained in groups of Swiss mice and SD rats (n = 60/sex/dose) exposed (via inhalation) at 0, 50, 200 or 600 ppm, six hours per day, five days per week, for 104 weeks. One lung squamous cell carcinoma was reported in a high dose male mouse. Several non-neoplastic lesions in mice were reported in the respiratory tract (olfactory epithelium atrophy, respiratory metaplasia, squamous metaplasia of respiratory epithelium in nasal cavity, tracheal epithelial hyperplasia). There was an increased incidence of squamous cell carcinoma in the nasal cavity in high dose female rats (4/59) compared with controls. There was a statistically significant increase in the total number of nasal tumours (benign and malignant) in high dose male rats. Non-neoplastic observations in rats included thinning of the olfactory epithelium of the nasal cavity, accompanied by basal cell hyperplasia (IARC, 1995).

Additional evidence of carcinogenicity in animals has been published since the IARC decision in 1995. Vinyl acetate administered to Wistar rats and Swiss mice at 5000 ppm in drinking water resulted in statistically significant increases in the percentage of animals with malignant tumours (cancers in the oral cavity, tongue, oesophagus and forestomach, and upper gastrointestinal tract). Female mice also showed tumours in the uterus at 5000 ppm (Soffritti *et al*., 2008).

Observation in humans

Respiratory irritation

Volunteers exposed to vinyl acetate at 19.4-71 ppm for 0.5-4 hours reported respiratory irritation. In workers exposed to vinyl acetate at average levels of 5-10 ppm (with possible acute exposures of 300 ppm), irritation of the throat and eyes was reported at levels of 21 ppm, but eye irritation was not reported under 10 ppm (ACGIH, 2001).

Carcinogenicity

In a cohort study of 4806 men employed at a chemical manufacturing plant in the USA between 1942-1973, the cohort had an excess risk of cancer (as compared to national rates) in the respiratory system. One subgroup, with undifferentiated large-cell lung cancer, had higher exposure to vinyl acetate (IARC, 1995).

A nested case-control study in the US investigated individuals who had died between 1940 and 1978 from certain cancers following exposure to 21 chemicals, including vinyl acetate. Potential exposure to vinyl acetate was reported for 7/52 deaths associated with non-Hodgkin's lymphoma, 3/20 deaths associated with multiple myeloma, 2/18 deaths associated with lymphocytic leukaemia and 2/39 deaths associated with non-lymphocytic leukaemia (IARC, 1995).

Reproduction and developmental toxicity

Based on the available data following oral and inhalation exposure in animals, vinyl acetate is not considered to cause reproductive or developmental toxicity. Developmental effects in rats were only observed at maternally toxic doses.

Public exposure

The critical health effects for vinyl acetate include local effects (respiratory irritation) and systemic long term effects (carcinogenicity and genotoxicity).

Vinyl acetate has domestic uses identified in Australia in adhesives, paints, lacquers and varnish, and possibly in automotive products. No use concentrations of vinyl acetate in these products are available. Based on these uses, the general public may be exposed to vinyl acetate via inhalation and/or dermal contact.

Vinyl acetate is highly volatile (vapour pressure = 90.2 mm Hg at 20^{o}C; ChemIDplus). Reducing the concentration in domestic products to result in vapour pressure similar to or below the assigned exposure standard for vinyl acetate (10 ppm time-weighted average (TWA); HSIS, SWA) may eliminate the risk of respiratory irritation from inhalation of chemical vapour.

From the calculation below, a concentration limit of about up to 1 % in domestic products is estimated to generate vapour concentration similar to the assigned TWA exposure standard for vinyl acetate:

Saturated vapour concentration for vinyl acetate at 100 % = 90.2/760 x 100 %

= 11.87 % or 118,700 ppm

Concentration required generating vapour pressure similar to 10 ppm TWA

= 100 %/118,700 ppm x 10 ppm

= 0.84 %

It is possible that vinyl acetate may be used in cosmetics in Australia, as it was allowed to be used as a film forming agent (concentration not available) in cosmetics in the EU until January 2015.

Pre-meeting public submissions

Two (2) public submissions were received that supported the proposal.

The main points provided in support of the amendment were:

- Vinyl Acetate may be present (typically as a residual monomer from synthesis of vinyl acetate copolymers) in both industrial and domestic goods and may also be present in some agricultural products.
- It was noted that the Schedule 6 entry due to be published 1 October 2018 may adversely impact a range of products currently on the market that were not identified during the consultation and consideration of vinyl acetate. These may include industrial and agricultural products.
- Clarification of the wording of the Schedule 6 entry would ensure a clear and consistent risk management approach is applied to domestic, industrial and agricultural products containing vinyl acetate that have the same risk profile.
- One submission noted that although the proposal is supported, a slight change to the terminology would ensure that domestic, industrial and agricultural uses are treated equally. These uses do not have intentional direct application to the body. This would minimise undue cost, ensure consistent seamless communication in the supply chain and maintain a balanced risk profile.

The public submissions will be made available on the TGA website.

Summary of ACCS-ACMS advice to the delegate

The committee recommended that the Schedule 6 entry for vinyl acetate be amended in the Poisons Standard as follows:

Schedule 6 – Amend Entry

VINYL ACETATE (excluding its derivatives) **except**:

a) in preparations for therapeutic use; or

b) in cosmetic preparations containing 0.01 per cent or less of vinyl acetate ~~as residual monomer in a polymer~~; or

c) in other preparations ~~for domestic use~~ containing 1 per cent or less of vinyl acetate.

The committee also recommended an implementation date of **1 October 2018,** to override the July 2017 decision.

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

The reasons for the advice were:

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

- Risks arise from evidence of carcinogenicity and mutagenicity. Although the evidence is limited, there is enough evidence to consider risk mitigation.
- Vinyl acetate is a monomer that is useful in a number of domestic formulations that require liquid consistency which polymerises or 'sets' to give a solid finish e.g. paints,

sealants, adhesives, etc. It is not expected to be a simple matter to replace this technology.

- There is a risk that non-cosmetic and non-therapeutic products will be captured inappropriately.
- Highly flammable.
- Risk of adverse respiratory health effects and carcinogenicity in humans.
- Domestic use has potential for general public to be exposed via vapour inhalation or dermal contact.
- Use of chemical in cosmetics banned in Europe from 2015.

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

- Vinyl acetate is used in paints, lacquers, varnishes, adhesives, sealants.
- Vinyl acetate is also a starting raw material in polymer production.
- Vinyl acetate may be present as an impurity in a wide range of products containing vinyl acetate polymers and copolymers, including in domestic products, cosmetics and therapeutic goods.
- Domestic use – widespread in the general population.
- Commercial/Industrial use – building, textile and paper.
- Confined space/inappropriate use and storage and skin contact.
- Potential variations or non-adherence to use and storage by general public.
- Possible cosmetic application to skin - Vinyl Acetate use in cosmetics in Australia not known, but may potentially be present in some nail varnish preparations.

c) the toxicity of a substance:

- Potential carcinogen, based on limited evidence of carcinogenicity in experimental animals.
- Potential mutagen (limited evidence), which may be due to formation of acetaldehyde (hydrolysis under aqueous conditions).
- Respiratory irritant.
- Respiratory irritancy, genotoxic potential at high doses and carcinogenic potential

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

- Can vary depending on product type and use for domestic products and in industrial manufacturing.
- Packaging and presentation as per proposed scheduling.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;

- ACCS-ACMS advice;
- Public submissions received;
- Scheduling Policy Framework (SPF 2018); and
- Section 52E(1) of the *Therapeutic Goods Act 1989* in particular: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

3. Advisory Committee on Chemicals Scheduling (ACCS #22)

3.1. Mefentrifluconazole

Delegate's interim decision

The delegate's interim decision is to create a new Schedule 5 entry for mefentrifluconazole in the Poisons Standard as follows:

Schedule 5 – New Entry

MEFENTRIFLUCONAZOLE **except** in preparations containing 7.5 per cent or less of mefentrifluconazole.

Proposed implementation date: 1 October 2018

The delegate considers the Committee's proposed implementation date of 1 October 2018 as being reasonable and appropriate in the circumstances.

Reasons:

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

- Benefit: Control of fungal disease in plants.

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

- Foliar spray of plant crops.

c) the toxicity of a substance:

- Skin sensitisation.
- Low acute toxicity for the product.

Scheduling proposal

The pre-meeting scheduling proposal for mefentrifluconazole was published on the TGA website 21 December 2017 at Consultation: Proposed Amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS-ACMS meetings, March 2018.

Background information for mefentrifluconazole

Referred scheduling proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the Poisons Standard with respect to mefentrifluconazole. The application proposes to exclude mefentrifluconazole from scheduling.

Scheduling application

The applicant's reasons for the proposal are:

- The available toxicity data for mefentrifluconazole is considered to be sufficient for the purposes of recommending a scheduling decision;
- Advice from the APVMA is that there are no objections on human health grounds for the approval of the active constituent; and
- The ACCS may consider that the toxicity hazard profile for acute exposure to mefentrifluconazole does not warrant scheduling.

Current scheduling status and scheduling history

Mefentrifluconazole is not scheduled in the Poisons Standard and has not been previously considered for scheduling. Therefore a scheduling history is not available.

Related triazole fungicides are in the Poisons Standard as follows:

Appendix B, Part 3

PROTHIOCONAZOLE.

Schedule 5

CYPROCONAZOLE **except** in preparations containing 10 per cent or less of cyproconazole.

DIFENOCONAZOLE.

EPOXICONAZOLE.

FENBUCONAZOLE.

HEXACONAZOLE **except** in preparations containing 5 per cent or less of hexaconazole.

IPCONAZOLE in preparations containing 2 per cent or less of ipconazole.

MYCLOBUTANIL.

PENCONAZOLE.

PROPICONAZOLE in preparations containing 20 per cent or less of propiconazole.

TEBUCONAZOLE.

TETRACONAZOLE in preparations containing 20 per cent or less of tetraconazole.

TRIADIMEFON in wettable powders containing 25 per cent or less of triadimefon.

TRIADIMENOL.

TRITICONAZOLE.

Schedule 6

FLUQUINCONAZOLE.

FLUTRIAFOL **except** in fertilisers containing 0.5 per cent or less of flutriafol.

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

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

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

TRIADIMEFON **except**:

a) when included in Schedule 5; or

b) in fertilisers containing 5 g/kg or less of triadimefon.

Australian regulations

Mefentrifluconazole is not approved in Australia. The proposed product is a suspension concentrate formulation containing 75 g/L mefentrifluconazole.

Mefentrifluconazole is not listed in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2018, and is not an excipient or active in any medicine on the Australian Register of Therapeutic Goods (ARTG).

International regulations

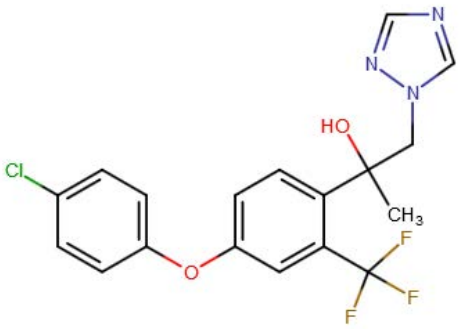
United States of America, Canada, Mexico and Brazil

Applications for the approval of mefentrifluconazole have been made.

European Union: Mefentrifluconazole has undergone public consultation and approval is pending according to Regulation (EC) No 1107/2009.

Substance summary

Table 3.1A: Chemical information for mefentrifluconazole

Property	Mefentrifluconazole
CAS name	alpha-[4-(4-chlorophenoxy)-2-(trifluoromethyl) phenyl]- alpha-methyl-1*H*-1,2,4-triazole-1-ethanol
CAS number	1417782-03-6
Chemical structure	
Molecular formula	$C_{18}H_{15}ClF_3N_3O_2$

Property	Mefentrifluconazole
Molecular weight	397.8 g/mol
IUPAC and/or common and/or other names	(2*RS*)-2-[4-(4-chlorophenoxy)-2- (trifluoromethyl)phenyl]-1-(1*H*-1,2,4-triazol-1-yl) propan-2-ol (IUPAC); Mefentrifluconazole (ISO); 1*H*-1,2,4-Triazole-1-ethanol, alpha-(4-(4-chlorophenoxy)-2-(trifluoromethyl)phenyl)-alpha-methyl-; 2-[4-(4-chloro-phenoxy)-2-trifluoromethyl-phenyl]-1-[1,2,4]triazol-1-yl-propan-2-ol

Mefentrifluconazole (ISO approved name) belongs to a new sub-group of triazole fungicides, the isopropanol azoles, due to its unique isopropanol moiety. It belongs to the group of sterol biosysthesis inhibitors in the sub group of demethylation inhibitors, which block ergosterol biosynthesis through inhibition of cytochrome P450 sterol 14-demethylase (Cyp51). The depletion of ergosterol and accumulation of non-functional 14-methyl sterols in the fungi results in inhibition of growth and cell membrane disruption.

The following information was extracted from the APVMA assessment report [Human Health Technical Report – mefentrifluconazole].

Table 3.1B: Acute toxicity end-points for mefentrifluconazole

Toxicity	Species	Mefentrifluconazole	SPF (2018) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000 (no deaths)	-
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>5000 (no deaths)	-
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	Rat	>5314 (no deaths)	-
Skin irritation	Rabbit	Non-irritating	-
Eye irritation	Rabbit	Non-irritating	-
Skin sensitisation (GPMT)	Guinea pig	Moderate sensitiser	5

Acute toxicity

Based on the available data from studies done according to OECD guidelines, mefentrifluconazole has low acute oral, dermal and inhalation toxicity in rats.

Skin and eye irritation

Based on available data from OECD guideline-compliant studies in rabbits, mefentrifluconazole is not a skin or eye irritant.

Sensitisation

An OECD guideline-compliant study shows that mefentrifluconazole is a moderate skin sensitiser in the guinea pig maximisation test.

Repeat-dose toxicity

A common, dominant finding in all mefentrifluconazole repeat dose studies is an increase in absolute and relative (to body weight) liver weights associated at higher doses with hepatocellular hypertrophy. In most studies, a simplistic interpretation of these findings would establish a no-observed-adverse-effect-level (NOAEL) at doses below those producing significant, adverse, toxicological effects. However, mode of action studies have demonstrated that mefentrifluconazole is an inducer of CYP450 in a partially phenobarbital like pattern. This is known to result in the liver effects observed with mefentrifluconazole across a range of species including in the rat, dog and non-human primate. These effects are generally recognised to be adaptive responses to a xenobiotic load and are not generally associated with progression to adverse histopathological or functional outcomes.

Evidence of hepatic effects consistent with enzyme induction (hepatocyte hypertrophy, increased liver weight) was modest in 28- and 90-day rat studies at doses of 388/334 and 256/314 mg/day in males/females in the 28 day and 90 day studies, respectively. For mefentrifluconazole, there is little evidence across the toxicological database of frank liver toxicity in rats or dogs.

The mechanistic data indicated that liver effects in C57BL/6J mice consisting of increased serum alanine transaminase (ALT) levels, increased liver weight, hypertrophy and liver cell proliferation are CAR-mediated, mouse specific and, in the absence of histologically demonstrable liver toxicity (necrosis) is likely to be of limited relevance for human risk assessment. Although the data do not indicate that liver effects are exclusively mediated by CAR-activation, it does indicate the mouse is likely to be more rather than less sensitive than humans.

Genotoxicity and carcinogenicity

There was no evidence that mefentrifluconazole was carcinogenic in mice and rats. Furthermore, mefentrifluconazole was tested for genotoxicity in an adequate range of *in vitro* and *in vivo* assays and based on these studies it is not genotoxic. Therefore, mefentrifluconazole does not warrant scheduling for these endpoints.

Reproduction and developmental toxicity

The NOAEL for general, systemic toxicity is 75 mg/kg/day for the F0 and F1 parental rats, based on decreased food consumption and body weight gain observed at 200 mg/kg/day. The NOAEL for fertility and reproductive performance for the parental rats is 200 mg/kg/day, the highest tested dose. The NOAEL for pup toxicity in the F1 and F2 generations is 75 mg/kg/day, based on pup mortality and the decrease in the pre-weaning pup body weights/pup weight gains observed at 200 mg/kg/day dose. Therefore, mefentrifluconazole is not a reproductive toxicant in rats.

In developmental studies, the effects of mefentrifluconazole in dams was limited to reduced body weight gains at 400 mg/kg/day in rats (NOAEL = 150 mg/kg/day) and no effects in rabbits at one half the LD_{50} (25 mg/kg) in non-pregnant rabbits. The NOAEL for fetal and developmental toxicity was at the highest dose tested in rats and rabbits (i.e. 400 and 25 mg/kg/day respectively). Mefentrifluconazole was not teratogenic in rats or rabbits.

Other toxicity studies

Neurotoxicity was investigated in rats by giving them a single dose of mefentrifluconazole up to 2000 mg/kg. Comprehensive behavioural and histopathological investigations revealed no evidence of neurotoxicity.

Observations in humans

No information available.

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS advice to the delegate

The committee recommended that a new Schedule 5 entry be created for mefentrifluconazole, as follows:

> **Schedule 5 – New Entry**
>
> MEFENTRIFLUCONAZOLE **except** in preparations containing 7.5 per cent or less of mefentrifluconazole.

The committee also recommended an implementation date of **1 October 2018**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the and extent of use; and (c) the toxicity of a substance.

The reasons for the advice were:

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

- Benefit: Control of fungal disease in plants.

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

- Foliar spray of plant crops.

c) the toxicity of a substance:

- Skin sensitisation.
- Low acute toxicity for the product.

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

- Nil.

e) the potential for abuse of a substance:

- Nil.

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

- Nil.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS advice;
- Scheduling Policy Framework (SPF 2018); and
- Section 52E(1) of the *Therapeutic Goods Act 1989* in particular: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; and (c) the toxicity of a substance.

3.2 Moxidectin

Delegate's interim decision

The delegate's interim decision is to amend the Schedules 6 and 4 entries for moxidectin in the Poisons Standard as follows:

Schedule 6 – Amend Entry

MOXIDECTIN:

a) in preparations for external use containing 2.5 per cent or less of moxidectin when packed in single dose tubes for the treatment of cats and dogs; or

b) in preparations for external use containing 2 per cent or less of moxidectin for the treatment of animals; or

c) in preparations for internal use containing 10 per cent or less of moxidectin for the treatment of sheep or cattle,

except when included in Schedule 5.

Schedule 4 – Amend Entry

MOXIDECTIN in preparations for injection containing 10 per cent or less of moxidectin **except** when included in Schedule 5 or 6.

Proposed implementation date: 1 October 2018

The delegate considers the Committee's proposed implementation date of 1 October 2018 as being reasonable and appropriate in the circumstances.

Reasons:

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

– Benefit: Increased access for use in sheep and cattle.

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

– Moxidectin is an antiparasitic drug which is intended for the treatment of endo- and ectoparasites in dogs, cats, cattle and sheep.

c) the toxicity of a substance:

– There is a lack of data supporting the request for an increase from 2 to 10 per cent in Schedule 5.

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

– The availability of the injectable substance at the requested concentration has the potential for harm that has not been addressed if Schedule 5.

Scheduling proposal

The pre-meeting scheduling proposal for moxidectin was published on the TGA website on 21 December 2017 at Consultation: Proposed Amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS-ACMS meetings, March 2018.

Background information for moxidectin

Referred scheduling proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the Poisons Standard with respect to moxidectin. The application proposes to amend the Schedule 4 entry for moxidectin by specifying the injection of 10% or less preparations for dogs and to amend the Schedule 5 entry for moxidectin by adding 10% or less injection preparations for sheep and cattle.

Scheduling application

The proposed amendments to the Poisons Standard are:

Schedule 5 – Amend Entry

MOXIDECTIN:

a) in preparations for external use for the treatment of animals other than cats and dogs, containing 0.5 per cent or less of moxidectin;

b) in preparations for external use for the treatment of cats and dogs, containing 2.5 per cent or less of moxidectin packed in single dose tubes with a volume of 1 mL or less; or

c) for internal use for the treatment of animals:

i) in divided preparations for dogs, containing 250 micrograms or less of moxidectin per dosage unit in a pack containing six or less dosage units; or

ii) in other preparations containing 2 per cent or less of moxidectin; or

d) in preparations for injection for the treatment of sheep and cattle, containing 10 per cent or less of moxidectin.

Schedule 4 – Amend Entry

MOXIDECTIN in preparations for injection ~~containing 10 per cent or less of moxidectin **except** when included in Schedule 5~~ for the treatment of dogs containing 10 per cent or less of moxidectin.

The applicant's reasons for the proposal are:

- Injectable preparations of moxidectin fall into Schedules 4 and 5. The Schedule 4 entry captures injections containing 10 per cent or less of moxidectin, except when included in Schedule 5. The Schedule 5 entry does not specifically make any reference to preparations for injection. However, in reviewing the scheduling history for moxidectin, it appears that Schedule 5 captures injections under the general description of '*for internal use for the treatment of animals …in other preparations containing 2 per cent or less of moxidectin*'. The Schedule 5 entry description is therefore not obvious for preparations for injection.

- The history of the scheduling of moxidectin (see Scheduling history) in preparations for injection indicates that the intent was to include the dog injection product in Schedule 4. This is due to the need for veterinary involvement and its presentation as a high concentration injectable that has a long-term effect achieved through a sustained release mechanism. The farm animal injection products remain in Schedule 5. The 2% cut-off in Schedule 5 was based on the concentration of moxidectin in the products that were considered when the entry was created. Due to the low potential for user exposure to moxidectin when using a ready-to-use injectable product for farm animals and farm animal injection products not being sustained release formulations like the dog injection product, the Schedule 5 cut-off for farm animal injection products can be increased from 2% to 10% to accommodate currently registered products.

Current scheduling status

Moxidectin is listed in Schedules 7, 6, 5 and 4 of the Poisons Standard as follows:

Schedule 7

MOXIDECTIN **except** when included in Schedule 4, 5 or 6.

Schedule 6

MOXIDECTIN for external use:

a) in preparations containing 2.5 per cent or less of moxidectin when packed in single dose tubes for the treatment of cats and dogs; or

b) in preparations containing 2 per cent or less of moxidectin for the treatment of animals,

except when included in Schedule 5.

Schedule 5

MOXIDECTIN:

a) in preparations for external use for the treatment of animals other than cats and dogs, containing 0.5 per cent or less of moxidectin;

b) in preparations for external use for the treatment of cats and dogs, containing 2.5 per cent or less of moxidectin packed in single dose tubes with a volume of 1 mL or less; or

c) for internal use for the treatment of animals:

i) in divided preparations for dogs, containing 250 micrograms or less of moxidectin per dosage unit in a pack containing six or less dosage units; or

ii) in other preparations containing 2 per cent or less of moxidectin.

Schedule 4

MOXIDECTIN in preparations for injection containing 10 per cent or less of moxidectin **except** when included in Schedule 5.

Scheduling history

In 1993, the Drugs and Poisons Schedule Committee (DPSC) agreed to include moxidectin in the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP). Due to the teratogenic effects of moxidectin and its similar chemical profile to abamectin, the committee decided to list moxidectin in Schedule 4 at 0.15% for use in dogs, Schedule 6 with a cut off of 1% or less for animal treatment and Schedule 7 with exceptions to the listings in Schedule 6 (for preparations <1% in animals) along with Appendix E and F listings.

In 1994 and 1995, the National Drugs and Poisons Schedule Committee (NDPSC) considered the rescheduling of '*moxidectin for use in dogs*' from Schedule 4 to Schedule 6. The NDPSC also considered a proposal to amend the Schedule 6 entry to capture a 2% oral horse worming preparation. As part of these rescheduling considerations, the Schedule 4 entry was deleted, the Schedule 5 entry was created and the Schedule 6 entry was amended. The Schedule 6 entry now only captures products containing ≤2% moxidectin for the external treatment of animals, while the Schedule 5 entry captures products for internal use (divided preparations for dogs, containing 140 µg or less of moxidectin per dosage unit in a pack containing 6 or less dosage units, and in other preparations containing 2% or less of moxidectin).

In May 1997, the NDPSC amended the Schedule 5 entry for internal use/divided preparations for dogs by increasing the concentration cut off to ≤250 µg moxidectin to capture a larger sized tablet for dogs.

In November 1999, the NDPSC considered an application to create a new Schedule 4 listing for an injectable formation containing ≤10% of moxidectin. The committee agreed that veterinary control of the 10% injection for dogs would be appropriate, based on moxidectin (as a high concentration injectable) having a long-term effect through a slow-release mechanism.

A review of the filaricides over several meetings from November 2000 through May 2001 confirmed the Schedule 5 entry for moxidectin in relation to the prophylaxis of heartworm in companion animals.

In 2002, the NDPSC considered a rescheduling application of moxidectin for spot-on products for companion animals. The committee amended the Schedule 6 entry to capture topical spot-on products for cats and dogs containing ≤2.5% moxidectin when packed in single dose tubes, based on the acute toxicity and potential for acute neurotoxicity.

In 2003, the NDPSC considered a rescheduling application for the Schedule 5 listing of moxidectin for pour-on preparations containing ≤0.5% moxidectin for application on cattle or deer. The committee agreed to amend the Schedule 5 and Schedule 6 entries for external use, so that the 0.5% pour-on for cattle was now captured in Schedule 5 (in preparations for external use for the treatment of non-companion animals containing 0.5% or less of moxidectin), due to low toxicity and use pattern limiting exposure to the public, while the ≤2.5% topical spot-on products for cats and dogs remained in Schedule 6.

In 2004, the NDPSC considered the rescheduling of ≤2.5% topical spot-on products for cats and dogs from Schedule 6 to Schedule 5, when in small pipette sizes (≤1 mL). The Schedule 5 entry was amended to include these smaller pipette sizes, while the larger sizes remained in Schedule 6. In addition, the Schedule 5 external use entry for '*non-companion animals*' containing 0.5% or less of moxidectin was reworded slightly to refer to '*animals other than cats and dogs*' ('*preparations for external use for the treatment of animals other than cats and dogs, containing 0.5% or less of moxidectin*').

In 2005, the NDPSC agreed to an editorial amendment to the Schedule 6 listing of moxidectin by moving '*except when included in Schedule 5*' from the end of Schedule 6, part (a) to the end of the Schedule 6 whole entry. This was to correct an inadvertent outcome of the previous wording,

whereby preparations containing ≤0.5% moxidectin for external use in the treatment of animals covered by Schedule 6 part (b) entry were also be captured by the Schedule 5, part (a) entry.

Australian regulations

Moxidectin is an APVMA-approved active constituent. Moxidectin is included as an active constituent in 89 registered veterinary products on the PubCRIS database for the treatment of parasites in/on animals. Formulation types and uses include topical pour-on products for cattle and deer (0.5%), topical spot-on products for dogs and cats (1-2.5%), oral tablets for dogs (30-204 μg/tablet), oral pastes/gels for horses (0.8-2%), oral drenches for sheep (0.1-0.2%), injectables combined with vaccine components for sheep (0.25-0.5%), injectables for cattle and sheep (1-10%), and an injectable for dogs (10%).

Moxidectin does not appear to be in any products on the Australian Register of Therapeutic Goods (ARTG).

Moxidectin does not appear in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2018.

International regulations

European Union (EU)

Moxidectin is approved in the EU Annex I of Council regulation No 237/90. The European Medicines Agency recently conducted an evaluation of the environmental impact of moxidectin-containing veterinary medicines. The Committee for Medicinal Products for Veterinary Use (CVMP) noted the importance of moxidectin use in the treatment of external parasites in cattle, sheep and horses. However, it also concluded that moxidectin fulfils the criteria of a persistent bio-accumulative toxin and poses a risk to the environment. The CVMP recommended risk mitigation measures and warnings to be included in product information including treatment to be only given when necessary.

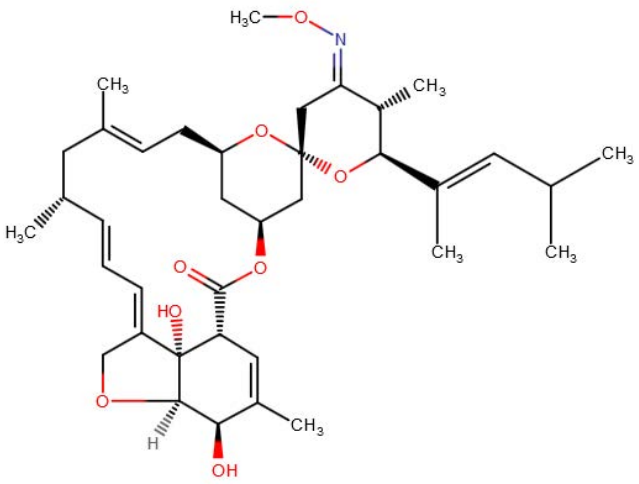
United States of America, Canada, and New Zealand

Moxidectin is registered for the treatment of animals.

Substance summary

Table 3.2A: Chemical information for moxidectin

Property	Moxidectin
CAS name	(6*R*,23*E*,25*S*)-5-*O*-demethyl-28-deoxy-25-[(1*E*)-1,3-dimethyl-1-butenyl]-6,28-epoxy-23-(methoxyimino)milbemycin B
CAS number	113507-06-5

Property	Moxidectin
Chemical structure	
Molecular formula	$C_{37}H_{53}NO_8$
Molecular weight	639.8 g/mol
IUPAC and/or common and/or other names	(6*R*,25*S*)-5-*O*-Demetyl-28-deoxy-25-[(*E*)-1,3-dimetyl-1-butenyl]-6,28-epoxy-23-oxomilbemycin B 23-(*E*)-(*O*-metyloxime) (WHO); Milbemycin B, 5-*O*-demetyl-28-deoxy-25-(1,3-dimetyl-1-butenyl)-6,28-epoxy-23-(metoxyimino)-, [6*R*,23*E*,25*S*(*E*)]- (USAN)

Acute toxicity

Not relevant – proposal is to clarify an ambiguity in the scheduling entry. No new toxicological information is provided.

Skin and eye irritation

Not relevant – proposal is to clarify an ambiguity in the scheduling entry. No new toxicological information is provided.

Skin sensitisation

Not relevant – proposal is to clarify an ambiguity in the scheduling entry. No new toxicological information is provided.

Repeat-dose toxicity, genotoxicity and carcinogenicity

Not relevant – proposal is to clarify an ambiguity in the scheduling entry. No new toxicological information is provided.

Reproduction and developmental toxicity

Not relevant – proposal is to clarify an ambiguity in the scheduling entry. No new toxicological information is provided.

Observation in humans

Not relevant – proposal is to clarify an ambiguity in the scheduling entry. No new toxicological information is provided.

Public exposure

Not relevant – proposal is to clarify an ambiguity in the scheduling entry. No new toxicological information is provided.

Pre-meeting public submissions

No public submissions were received.

Summary of ACCS advice to the delegate

The committee recommended that the Schedules 6 and 4 entries be amended for moxidectin, as follows:

Schedule 6 – Amend Entry

MOXIDECTIN:

a) in preparations for external use containing 2.5 per cent or less of moxidectin when packed in single dose tubes for the treatment of cats and dogs; or

b) in preparations for external use containing 2 per cent or less of moxidectin for the treatment of animals; or

c) in preparations for internal use containing 10 per cent or less of moxidectin for the treatment of sheep or cattle,

except when included in Schedule 5.

Schedule 4 – Amend Entry

MOXIDECTIN in preparations for injection containing 10 per cent or less of moxidectin **except** when included in Schedule 5 or 6.

The committee also recommended an implementation date of **1 October 2018**.

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

The reasons for the advice were:

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

– Benefit: Increased access for use in sheep and cattle.

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

– Moxidectin is an antiparasitic drug which is intended for the treatment of endo- and ectoparasites in dogs, cats, cattle and sheep.

c) the toxicity of a substance:

- There is a lack of data supporting the request for an increase from 2 to 10 per cent in Schedule 5.

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

- The availability of the injectable substance at the requested concentration has the potential for harm that has not been addressed if Schedule 5.

e) the potential for abuse of a substance:

- Nil.

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

- Nil.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS advice;
- Scheduling Policy Framework (SPF 2018); and
- Section 52E(1) of the *Therapeutic Goods Act 1989* in particular: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

3.3 Eprinomectin

Delegate's interim decision

The delegate's interim decision is to amend the Poisons Standard by creating a new Schedule 6 entry for eprinomectin and amending the Schedule 7 entry to reflect this change as follows:

Schedule 6 – New Entry

EPRINOMECTIN for internal use in preparations containing 5 per cent or less of eprinomectin **except** when included in Schedule 5.

Schedule 7 – Amend Entry

EPRINOMECTIN **except** when included in Schedule 5 or 6.

Proposed implementation date: 1 October 2018

The delegate considers the Committee's proposed implementation date of 1 October 2018 as being reasonable and appropriate in the circumstances.

Reasons:

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate for the decision include:

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

- Benefits: control of parasites in animals and the increased availability for use by farmers.
- Risks: Accidental self-injection may result in injury due to moderate acute oral/dermal toxicity.

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

- Only limited quantities are available for exposure at a single time, thus limiting risk of accidental self-injection.
- Product will be sold through retailers servicing the rural cattle industry and not directly to the public or through retail outlets normally serving the public.

c) the toxicity of a substance:

- High acute oral and dermal toxicity resulting in neurological toxicity. Repeat dose toxicity NOAEL 0.8-5 mg/kg in rats/dogs.

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

- When packed as a divided dose preparation, exposure is highly controlled. The packaging and labelling are under APVMA control.
- Topical preparation for use on animals and long-acting injection. APVMA regulated product.

Scheduling proposal

The pre-meeting scheduling proposal for eprinomectin was published on the TGA website on 21 December 2017 at Consultation: Proposed Amendments to the Poisons Standard - ACCS, ACMS and Joint ACCS-ACMS meetings, March 2018.

Background information for eprinomectin

Referred scheduling proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the Poisons Standard with respect to eprinomectin. The application proposes to amend the Schedule 5 entry for eprinomectin to include '*for internal use*' and to increase the cut-off from 0.5% to 5%.

Scheduling application

The proposed amendments to the Poisons Standard are:

> **Schedule 5 – Amend Entry**
>
> EPRINOMECTIN in preparations for internal use containing ~~0.~~5 per cent or less of eprinomectin.

The applicant's reasons for the request are:

- The scheduling delegate may consider that the risk, hazard profile and presentation of the injectable eprinomectin product supports a proposed cut-off to Schedule 5.
- Injectable avermectin-based products (e.g. ivermectin, doramectin) that do not require veterinarian oversight have entries in Schedule 5.
- Registration of the injectable product containing 5% eprinomectin in Australia is pending.

Current scheduling status

Eprinomectin is listed in Schedules 5 and 7 of the Poisons Standard as follows:

> **Schedule 7**
>
> EPRINOMECTIN **except** when included in Schedule 5.
>
> **Schedule 5**
>
> EPRINOMECTIN in preparations containing 0.5 per cent or less of eprinomectin.

Related substances that are in the Poisons Standard as follows:

> **Schedule 7**
>
> ABAMECTIN **except** when included in Schedule 5 or 6.
>
> DORAMECTIN **except** when included in Schedule 5 or 6.
>
> EMAMECTIN **except** when included in Schedule 5 or 6.
>
> IVERMECTIN **except** when included in Schedule 4 or 5.
>
> MOXIDECTIN **except** when included in Schedule 4, 5 or 6.

Schedule 6

ABAMECTIN:

a) in preparations for pesticidal use containing 4 per cent or less of abamectin except when included in Schedule 5; or

b) in slow-release plastic matrix ear tags for livestock use containing 1 g or less of abamectin.

DORAMECTIN for external use for the treatment of animals, in preparations containing 2 per cent or less of doramectin.

EMAMECTIN in preparations containing 5 per cent or less of emamectin **except** when included in Schedule 5.

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

MOXIDECTIN for external use:

a) in preparations containing 2.5 per cent or less of moxidectin when packed in single dose tubes for the treatment of cats and dogs; or

b) in preparations containing 2 per cent or less of moxidectin for the treatment of animals,

except when included in Schedule 5.

Schedule 5

ABAMECTIN

a) in preparations, for internal use for the treatment of animals, containing 1 per cent or less of abamectin; or

b) in gel formulations containing 0.05 per cent or less of abamectin in applicators containing 50 mg or less of abamectin.

DORAMECTIN for internal use for the treatment of animals, in preparations containing 2 per cent or less of doramectin.

EMAMECTIN in preparations containing 2 per cent or less of emamectin.

IVERMECTIN for use in animals:

a) in preparations for the prophylaxis of heartworm in cats and dogs;

b) in intraruminal implants containing 160 mg or less of ivermectin;

c) in preparations containing 3.5 per cent or less of ivermectin when packed in child-resistant packaging or in packaging approved by the relevant registration authority; or

d) in other preparations containing 2 per cent or less of ivermectin.

MILBEMECTIN in preparations containing 1 per cent or less of milbemectin.

MOXIDECTIN:

a) in preparations for external use for the treatment of animals other than cats and dogs, containing 0.5 per cent or less of moxidectin;

b) in preparations for external use for the treatment of cats and dogs, containing 2.5 per cent or less of moxidectin packed in single dose tubes with a volume of 1 mL or less; or

c) for internal use for the treatment of animals:

i) in divided preparations for dogs, containing 250 micrograms or less of moxidectin per dosage unit in a pack containing six or less dosage units; or

ii) in other preparations containing 2 per cent or less of moxidectin.

SELAMECTIN **except** in preparations containing 12 per cent or less of selamectin.

Schedule 4

IVERMECTIN

a) for human use; or

b) for the treatment of mange in dogs.

Appendix J, Part 2

ABAMECTIN

Condition: 1 (Not to be available **except** to authorised or licensed persons.)

Scheduling history

In August 1997, the National Drugs and Poisons Scheduling Committee (NDPSC) considered an application to schedule eprinomectin, a new semi-synthetic second generation avermectin. Due to the similarities in structure and metabolism of eprinomectin and emamectin, the toxicological data for emamectin was used to support the scheduling application for eprinomectin. The committee decided to place eprinomectin in Schedule 7 with a cut-off to Schedule 5 at 0.5%, based on the toxicological data and uncertainties around neurotoxicity related hypersensitivity, as observed in a sub-population of CF-1 mice.

Australian regulations

Eprinomectin does not appear to be in any products on the Australian Register of Therapeutic Goods (ARTG).

Eprinomectin does not appear in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2018.

Eprinomectin is approved by the APVMA in four (4) pour-on (topical) veterinary parasiticide products in beef and dairy cattle and deer.

International regulations

United States of America

Eprinomectin 5% in an extended release injectable parasiticide for cattle, at 1 mg/kg by subcutaneous injection (approved September 2011; Food and Drug Administration New Animal Drug Application 141-327).

European Union

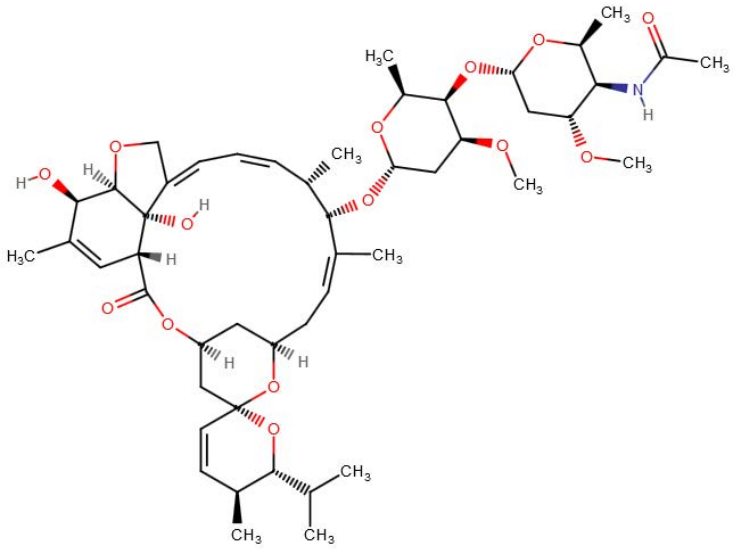
The European Medicines Agency included eprinomectin in Annex I of Council Regulation (No 2377/90) in 1996 and recommends a dosage regimen is a single dose of 0.5 mg/kg applied topically.

New Zealand

Eprinomectin is permitted as a pour-on solution at 0.5% for cattle and deer.

Substance summary

Table 3.3A: Chemical information for eprinomectin

Property	Eprinomectin
CAS name	(4")-4"-acetylamino-4"-deoxyavermectin B1a
CAS numbers	123997-26-2 (eprinomectin B1a is 133305-88-1, eprinomectin B1b is 133305-89-2)
Chemical structure	
Molecular formula	$C_{50}H_{75}O_{14}$
Molecular weight	900.1 g/mol
IUPAC and/or common and/or other names	Mixture of eprinomectins B1a and B1b (2a*E*,4*E*,8*E*)-(5′*S*,6*S*,6′*R*,7*S*,11*R*,13*S*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-6′-[(*S*)-sec-butyl]-5′,6,6′,7,10,11,14,15,17a,20,20a,20b-dodecahydro-20,20b-dihydroxy-5′,6,8,19-tetramethyl-17-oxospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-pq][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-7-yl 4-*O*-(4-acetamido-2,4,6-trideoxy-3-*O*-methyl-α-*L*-lyxo-hexopyranosyl)-2,6-dideoxy-3-*O*-methyl-α-*L*-arabino-hexopyranoside (major component)

Property	Eprinomectin
	(2a*E*,4*E*,8*E*)-(5′*S*,6*S*,6′*R*,7*S*,11*R*,13*S*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-5′,6,6′,7,10,11,14,15,17a,20,20a,20b-dodecahydro-20,20b-dihydroxy-6′-isopropyl-5′,6,8,19-tetramethyl-17-oxospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-pq][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-7-yl 4-*O*-(4-acetamido-2,4,6-trideoxy-3-*O*-methyl-α-*L*-lyxo-hexopyranosyl)-2,6-dideoxy-3-*O*-methyl-α-*L*-arabino-hexopyranoside (minor component)

Table 3.3B: Acute toxicity end-points for eprinomectin

Toxicity	Species	Eprinomectin	SPF (2018) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat Mouse	55 (female) 70 (female)	Schedule 6-7
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat Rabbit	>660 460	Schedule 6
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rat	5110	-
Skin irritation	Rabbit	Not irritating [a]	-
Eye irritation	Rabbit	Irritant	Schedule 6
Skin sensitisation (GPMT)	Guinea pig	Negative	-

Acute toxicity

The acute toxicity of eprinomectin is moderate. Central nervous system clinical signs were the most notable findings in acute toxicity studies when administered at high doses.

Skin irritation

Limited information indicates that eprinomectin is not a skin irritant in rabbits.

Eye irritation

There are reports that it may be an irritant to eyes. Other avermectins (e.g. emamectin, moxidectin) are classified as moderate/severe eye irritants.

Sensitization

Eprinomectin is not a skin sensitiser in the guinea pig (GPMT).

Repeat-dose toxicity

Major findings in the repeat dose studies in both rats and dogs were neurological clinical signs and neurological histopathological changes.

In a 14-week dietary toxicity study in rats, the NOAEL was 5 mg/kg/day based on body tremors, decreased weight gain, decreased urine output, increased organ weights (adrenal, liver, uterus and pituitary), decreased ovarian weight, and sciatic nerve degeneration in some animals at 20/30 mg/kg/day.

In a 14-week oral (gavage) toxicity study in dogs, the NOAEL was 0.8 mg/kg/day based on reduced body weight gain and sciatic nerve degeneration at dose levels of 1.6/2.4 mg/kg/day.

In a 53-week oral (gavage) toxicity study in dogs, the NOAEL was 1 mg/kg/day, based on clinical signs e.g. transient mydriasis, and slight neuronal degeneration at higher doses.

The data package for eprinomectin lacked a long-term rodent study. This was discussed at the time of the initial risk assessment of eprinomectin with the Applicant. It was concluded in that initial assessment that due to the structural and metabolic similarities of eprinomectin and emamectin, the toxicological data for emamectin, which includes a chronic toxicity rodent study, as well as carcinogenicity studies, could be used to support the scheduling application for eprinomectin. Moreover, it was noted that both compounds are produced from abamectin by replacement of the 4´-hydroxyl group (with an epi-acetylamino moiety for eprinomectin and an epi-methylamino moiety for emamectin) and that the metabolism of both compounds is limited to deacetylation of the 4´ acetyl group for eprinomectin and deamination at the same position for emamectin.

Given the similarities of eprinomectin and emamectin, it is of relevance to note the toxicological findings for the latter compound. The following data were taken from the European Agency for the Evaluation of Medicinal Products (EMA) Committee for Veterinary Medicinal Products (CVMP) Emamectin Summary Report.

Repeat dose toxicity studies in rats with emamectin included 14-week and 53-week dietary studies. In the 14-week study at doses of 0, 0.25, 1 and 5 mg/kg/day, all males and most females given 5 mg/kg/day showed neuronal vacuolation/degeneration of the brain, spinal cord and sciatic nerve. The NOEL was 1 mg/kg/day. In the 53-week study at doses of 0, 0.1, 1 and 2.5/5 mg/kg/day (high-dose females were given 5 mg/kg/day up to week 18; males were given 2.5 mg/kg/day throughout), neuronal degeneration of the brain and spinal cord was observed in males given 2.5 mg/kg/day and females given 2.5/5 mg/kg/day. The NOEL was 1 mg/kg/day.

Repeat dose toxicity studies in dogs with emamectin included 14-week and 53-week gavage studies. In the 14-week study at doses of 0, 0.25, 0.5 and 1 mg/kg/day (up to the start of week 3, doses were 0, 0.5, 1 and 1.5 mg/kg/day, the NOEL was 0.25 mg/kg/day based on neuronal degeneration (as well as skeletal muscle atrophy) at doses ≥0.5 mg/kg/day. In the 53-week study, at doses of 0, 0.25, 0.5, 0.75 and 1 mg/kg/day, the NOEL was also 0.25 mg/kg/day, with axonal degeneration in the CNS and PNS seen at doses of ≥0.5 mg/kg/day.

Thus, dogs were more sensitive than rats to the neuronal histopathological changes induced by emamectin. As the same appears to be the case with eprinomectin, the lack on a chronic rat toxicity study did not impact on the selection of an NOAEL for the risk assessment.

Genotoxicity

Eprinomectin was tested for genotoxicity in an adequate range of *in vitro* and *in vivo* assays and based on these studies eprinomectin was not considered to be genotoxic. This finding has also been shown from other avermectins.

Carcinogenicity

Carcinogenicity studies have not been conducted on eprinomectin. The avermectins are closely related structurally and appear to share a common mechanism of action and mechanism of

mammalian toxicity. None of the avermectins has been found to be genotoxic and none possess a structural relationship to known carcinogens. Carcinogenicity studies on abamectin, emamectin and moxidectin (avermectins structurally related to eprinomectin) did not reveal any carcinogenic potential. The negative carcinogenicity findings for emamectin were considered as supporting evidence for the likely lack of carcinogenic hazard of eprinomectin in previous assessments by the APVMA.

Given the above evidence/arguments, it is concluded that a carcinogenic risk for eprinomectin is unlikely.

Reproduction and developmental toxicity

In a two-generation reproductive toxicity study in rats given eprinomectin in the diet, the NOAEL for maternal toxicity and reproductive toxicity was 1.5 mg/kg bw/d, based on reduced body weight gain, reduced food consumption and reduced fecundity at 4.5 mg/kg/day. The NOAEL for offspring toxicity was 0.8 mg/kg/day based on tremors and reduced body weight in pups at higher doses.

In a developmental toxicity study in rats given eprinomectin via gavage, the NOAEL for maternal toxicity was 1 mg/kg/day based on increased maternal body weight at the doses of 3 mg/kg/day and higher. The NOAEL for embryofetal toxicity was 12 mg/kg/day, the highest dose tested.

In two developmental toxicity studies in rabbits given eprinomectin via gavage, the NOAEL for maternal toxicity was 0.5 and 2 mg/kg/day based on reduced pupillary reflexes or mydriasis at higher doses. The NOAEL for embryofetal toxicity was 2 mg/kg/day (highest dose tested) in one study and 8 mg/kg/day (highest dose tested) in the second study.

Overall, Eprinomectin showed no evidence of embryofetal toxicity or teratogenicity in rat and rabbit developmental toxicity studies.

Observation in humans

Eprinomectin is not used as a human medicine. The related drug, ivermectin, is used clinically in humans for treating various diseases/infestations e.g. onchocerciasis (river blindness), lymphatic filariasis, strongyloidiasis, head lice and scabies.

Public exposure

Eprinomectin-containing products for use on food-producing animals are registered for use in Australia by the APVMA. Very limited public exposure to eprinomectin would be expected, as current uses are limited to use on farms.

Pre-meeting public submissions

One (1) public submission was received, which opposed the proposal.

The main points provided in opposition of the amendment were:

- The addition of 'for internal use' to the Schedule 5 entry would result in currently registered external use eprinomectin-based veterinary products being excluded from Schedule 5, resulting in them being captured by the Schedule 7 entry.
- The proposed scheduling change that will exclude external use products may be unintentional. However, if it is not, a rationale for the exclusion of external use products is requested.

The public submission will be made available on the TGA website.

Summary of ACCS advice to the delegate

The committee recommended that a new Schedule 6 entry for eprinomectin be created and the Schedule 7 entry amended to reflect this change, as follows:

> **Schedule 6 – New Entry**
>
> EPRINOMECTIN for internal use in preparations containing 5 per cent or less of eprinomectin **except** when included in Schedule 5.
>
> **Schedule 7 – Amend Entry**
>
> EPRINOMECTIN **except** when included in Schedule 5 or 6.

The committee also recommended an implementation date of **1 October 2018**.

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

The reasons for the advice were:

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

- Benefits: control of parasites in animals and the increased availability for use by farmers.
- Risks: Accidental self-injection may result in injury due to moderate acute oral/dermal toxicity.

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

- Only limited quantities are available for exposure at a single time, thus limiting risk of accidental self-injection.
- Product will be sold through retailers servicing the rural cattle industry and not directly to the public or through retail outlets normally serving the public.

c) the toxicity of a substance:

- High acute oral and dermal toxicity resulting in neurological toxicity. Repeat dose toxicity NOAEL 0.8-5 mg/kg in rats/dogs.

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

- When packed as a divided dose preparation, exposure is highly controlled. The packaging and labelling are under APVMA control.
- Topical preparation for use on animals and long-acting injection. APVMA regulated product.

e) the potential for abuse of a substance:

- Nil.

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

- Nil.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal;
- ACCS advice;
- Scheduling Policy Framework (SPF 2018); and
- Section 52E(1) of the *Therapeutic Goods Act 1989* in particular: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.