



Australian Government

Department of Health

Therapeutic Goods Administration

Notice of interim decisions made under Regulation 42ZCZN of the *Therapeutic Goods Regulations 1990*

12 September 2019

This web publication constitutes a notice for the purposes of regulation 42ZCZP of the *Therapeutic Goods Regulations 1990* (the **Regulations**). In accordance with regulation 42ZCZP, this notice sets out:

- the interim decisions made by a delegate of the Secretary under regulation 42ZCZN in relation to proposed amendments to the current Poisons Standard which were referred to an expert advisory committee under subdivision 3D.2 of the Regulations in June 2019;
- the proposed date of effect of the proposed amendments (in circumstances where the interim decision proposes an amendment to the current Poisons Standard).

In accordance with regulation 42ZCZP, interested persons (including the applicant requesting the amendment) are invited to make submissions to the Secretary in relation to these interim decisions on or before 10 October 2019.

Persons making submissions are strongly encouraged to lodge submissions in an electronic format (word or unsecured PDF preferred) using the public submission coversheet available on the [TGA's website](#). Where possible, submissions should be sent to the email addresses provided below:

- chemicals.scheduling@health.gov.au (for submissions relating to interim decisions made in relation to proposed amendments referred to the Advisory Committee on Chemicals Scheduling);
or
- medicines.scheduling@health.gov.au (for submissions relating to interim decisions made in relation to proposed amendments referred to the Advisory Committee on Medicines Scheduling or the Advisory Committee on Medicines and Chemicals Scheduling in joint session).

Please note that in accordance with subregulation 42ZCZQ(4) of the Regulations, the Secretary must publish all relevant submissions received. The Secretary must not, however (pursuant to subregulation 42ZCZQ(5)), publish any information that the Secretary considers to be confidential information.

1 Interim decisions on proposed amendments referred to the Advisory Committee on Medicines Scheduling (ACMS #27, June 2019)

1.1. Interim decision in relation to phenpromethamine

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to phenpromethamine as follows:

Schedule 10 – New Entry

PHENPROMETHAMINE.

Index – New Entry

PHENPROMETHAMINE

Schedule 10

Proposed date of effect of the proposed amendment

1 February 2020

Reasons for the interim decision (including findings on material questions of fact)

Applicant's scheduling proposal and reasons for the proposal

An application to create a Schedule 10 entry for phenpromethamine was considered.

The Applicant's proposed amendments to the Poisons Standard were:

Schedule 10 – New Entry

PHENPROMETHAMINE.

Index – New Entry

PHENPROMETHAMINE

Schedule 10

The Applicant's main points provided in support of the proposed amendments were as follows:

- Phenpromethamine is considered a primary analogue of methamphetamine (structural isomers) as per section 301.9 of the *Criminal Code Act 1995*. Phenpromethamine is a stimulant; it is chemically and structurally related to amphetamine, its derivatives (e.g. methamphetamine) and analogues.
- Phenpromethamine is a substance prohibited from sport by the World Anti-Doping Agency (WADA).
- Phenpromethamine is currently controlled by the German regulator *Betäubungsmittelgesetz* (BtMG) and is classified as Anlage I, non-tradeable substances available only by special permission of the authorities, which is granted for scientific or other public interest purposes.
- Phenpromethamine has been reported to the Early Warning Advisory on New Psychoactive Substances of the United Nations Office on Drugs and Crime (UNODC).
- Article 10 of the UNESCO International Convention against Doping in Sport obliges State Parties (including the Australian Government) to encourage producers and distributors of nutritional supplements to establish best practices in the marketing and distribution of nutritional supplements, including information regarding their analytic composition and quality assurance. The marketplace supplies thousands of products claiming to provide nutritional support for

athletes. However, there are growing concerns about the prevalence and quality control of these supplements. This is because supplements may contain substances that are prohibited from sport and/or it is often unknown what a supplement actually contains. Athletes cannot be sure if a supplement contains substances that are prohibited from sport or understand the potential health Current scheduling status

Current scheduling status

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

Australian regulations

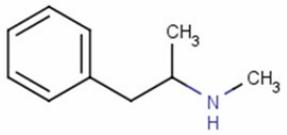
- Phenpromethamine is not listed on the [TGA Ingredient Database](#).
- There are no medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#)¹ that contain phenpromethamine as an active ingredient.
- Phenpromethamine is not permitted to be included in listed medicines as it is not included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 2 of 2019](#)².
- The [Database of Adverse Event Notifications \(DAEN\)](#)³ contains no reports of adverse events for products containing phenpromethamine as an active ingredient.
- There are no products containing phenpromethamine listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#)⁴.

International regulations

- Phenpromethamine is prohibited from sport under the 'S6: Stimulants' of the WADA List of Prohibited Substances and Methods as a result of its purported stimulant properties due to its structural relationship to amphetamine, its derivatives (e.g. methamphetamine) and analogues (WADA 2019).
- Phenpromethamine is currently controlled in Germany by the Betäubungsmittelgesetz (BtMG) and is classified as Anlage I, non-tradeable substances available only by special permission of the authorities, which is granted only for scientific or other public interest purposes (BtMG 2019).
- The [European Chemicals Agency \(ECHA\)](#) hazard classification for phenpromethamine is, 'Danger! According to the classification provided by companies to ECHA in CLP notifications this substance is harmful if swallowed, causes serious eye damage, causes skin irritation and may cause respiratory irritation'.

Substance summary

Table 1: Chemical information for phenpromethamine

Property	Phenpromethamine
Chemical structure	
Molecular formula	C ₁₀ H ₁₅ N

¹ <https://www.tga.gov.au/artg>

² <https://www.legislation.gov.au/Details/F2019L00834>

³ <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

⁴ <https://portal.apvma.gov.au/pubcris>

Molecular weight	149.23 g/mol
CAS name	<i>N</i> -methyl-2-phenylpropan-1-amine
CAS number	93-88-9
IUPAC and/or common and/or other names	<i>N</i> -methyl-2-phenylpropylamine (IUPAC), benzeneethanamine, <i>N</i> , <i>beta</i> -dimethyl- (9CI), <i>N</i> , <i>beta</i> -dimethylphenethylamine, <i>N</i> , <i>beta</i> -dimethyl, 1-methylamino-2-methyl-2-phenylethane, 1-methylamino-2-phenylpropane, 1-phenyl-1-methyl-2-methylamino-ethan, 1-phenyl-1-methyl-2-ethylaminoethane, fenprometamina, phenpromethaminum, phenylpropylmethylamine, vonedrine, <i>N</i> , <i>beta</i> -dimethylphenethylamine, phenpromethadrinum

Summary of pre-meeting public submissions

Two (2) submissions were received in response to [the notice published under regulation 42ZCZK advising of the proposed amendment](#). Both were in support of the proposed amendment.

The main points in support of the proposed amendment were:

- Phenpromethamine is a member of the phenethylamine family which acts as a central nervous system stimulant.
- Phenpromethamine is prohibited by the World Anti-Doping Agency (WADA) as a stimulant.
- There has been an increase in calls to the NSW Poisons Information Centre (PIC) regarding exposures to weight-loss and body building products in the past 5 years and most of these calls required medical attention (57%).

Year	Calls to NSW PIC on body building/weight-loss products
2014	57
2015	66
2016	68
2017	79
2018	59
Jan-April 2019	30

- There is often little detail of the contents of weight-loss and body building products. However, once ingested, they commonly show signs of stimulant toxicity.
- Entry of phenpromethamine in Schedule 10 will minimise the opportunity of it being included in weight-loss and bodybuilding products.

Summary of ACMS advice/recommendations to the Delegate

The Committee recommended that a Schedule 10 entry for phenpromethamine be created as follows:

Schedule 10 – New Entry

PHENPROMETHAMINE.

Index – New Entry

PHENPROMETHAMINE

Schedule 10

The Committee also recommended an implementation date as soon as practicable.

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; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice included:

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

- Side effects of phenpromethamine are expected to be similar to other stimulants such as methamphetamine (cardiovascular side effects of most concern).
- Member of the phenethylamine family and primary analogue of methamphetamine; phenpromethamine has the potential to cause harm based on its chemical profile.
- Limited research informs the risk or benefits (no current registered therapeutic product in use).
- Preclinical studies (in cats) have demonstrated a pressor effect.

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

- No currently established therapeutic use.
- Used by the broader community as a stimulant in ‘pre-workout’ sports supplements/stimulants typically ingested before physical activity.
- Stated purpose for use of sports supplements (in general) is to provide a stimulant effect, to improve athletic performance, and to increase weight loss, though the ingredient is not listed on products.

(c) the toxicity of a substance:

- Limited peer-reviewed studies assessing toxicity in humans; plausible toxicity based on its structural analogues (methamphetamine) and stimulant properties.
- It is a non-approved drug with little information about its safety.

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

- There are currently no ARTG registered products containing phenpromethamine as an active ingredient and it is not permitted to be included in listed medicines.
- There are also no veterinary products containing this substance.

(e) the potential for abuse of a substance:

- Phenpromethamine is considered to have a potential for abuse due to its stimulant properties arising from its structural relationship to amphetamine, its derivatives and analogues.

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

- There are broader concerns related to the manufacture, labelling, ingredients and use of sports supplements that go beyond the concerns with phenpromethamine, but are relevant to consider in the context of public health.
- Scheduling is important to avoid inadvertent consumption and related harms given it has been identified in products where it was not labelled.

- Phenpromethamine is considered to be a new psychoactive substance which may pose increasing and serious harms to public health.
- XXX
- Available information suggests this segment of the sports supplement industry is considerably expanding in Australia.

Delegate's considerations

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to phenpromethamine;
- Advisory Committee on Medicines Scheduling's advice;
- The public submissions received before the [first closing date](#);
- Section 52E of the *Therapeutic Goods Act 1989*, in particular: (a) 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;
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- The Australian Health Ministers' Advisory Council's [Scheduling Handbook](#) (V 1.0, January 2018).

Reasons for the interim decision

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (a) 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.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the scheduling factors for Schedule 8, Schedule 9 and Schedule 10.

I have made a decision to amend the current Poisons Standard by creating a new Schedule 10 entry for phenpromethamine and I have set out my reasons below.

Having considered the SPF 2018, it is my view that phenpromethamine meets some of the Schedule 9 scheduling factors on the grounds that *'The substance has no currently established therapeutic value and is likely to present a high risk of dependency, abuse, misuse or illicit use'*. However, in my view, these are minor considerations as the evidence for these harms have been extrapolated from analogues and are based on its stimulant properties. Further, whilst phenpromethamine is a structural analogue of methamphetamine (which is a Schedule 8 substance) and given the lack of evidence to support its therapeutic use, I do not believe it meets the scheduling factors for Schedule 8.

In making my decision, I considered the scheduling factors for inclusion in Schedule 10, particularly *'the substance poses such a high public health risk, including potential risk, that its sale, supply and/or use require very strict control, with access generally being prohibited'*. Phenpromethamine is a phenethylamine, a class of substances with documented psychoactive and stimulant health effects and I find that the risk of cardiovascular outcomes following use of phenpromethamine to be a significant potential risk to public health.

I have considered that inclusion in Schedule 10 is a public health measure, given that it XXX, is banned by the World Anti-Doping Agency (WADA) and that minimal evidence exists for its use in humans. I have also had regard for the potential risk of inadvertent use in unlabelled sports supplements and the related harms. Placing phenpromethamine in Schedule 10 would mitigate such risks. I note that scheduling phenpromethamine in Schedule 10 is consistent with the scheduling of similar substances such as 1,3-dimethylamylamine (DMAA).

1.2. Interim decision in relation to 1,4-Dimethylpentylamine (DMPA)

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to 1,4-dimethylpentylamine (DMPA) as follows:

Schedule 10 – New Entry

1,4-DIMETHYLPENTYLAMINE (DMPA).

Index – New Entry

1,4-DIMETHYLPENTYLAMINE (DMPA)

Schedule 10

Index – Amend Entry

ALKYLAMINES WITH STIMULANT PROPERTIES

cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisooheptane, DMHA, 1,5-dimethylhexylamine, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane citrate (AMP citrate), 1,4-dimethylpentylamine, DMPA.

Schedule 10

Proposed date of effect of the proposed amendment

1 February 2020

Reasons for the interim decision (including findings on material questions of fact)

Applicant's scheduling proposal and reasons for the proposal

An application to create a Schedule 10 entry for DMPA was considered.

The Applicant's proposed amendments to the Poisons Standard were:

Schedule 10 – New Entry

1,4-DIMETHYLPENTYLAMINE (DMPA).

Index – New Entry

1,4-DIMETHYLPENTYLAMINE (DMPA)

Schedule 10

Index – Amend Entry

ALKYLAMINES WITH STIMULANT PROPERTIES

cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisooheptane, DMHA, 1,5-dimethylhexylamine, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane citrate (AMP citrate), 1,4-dimethylpentylamine, DMPA.

Schedule 10

The Applicant's main points provided in support of the proposed amendments were as follows:

- 1,4-Dimethylpentylamine (DMPA) is currently captured under the Schedule 10 entry for 'Alkylamines with stimulant properties' due to its similarities to 1,3-dimethylamylamine (DMAA) and 1,3-dimethylbutylamine (DMBA).
- In order to remove any potential ambiguity about the scheduling status of DMPA, it is proposed that a new Schedule 10 entry be created for DMPA. This would characterise DMPA as a substance of such danger to health as to warrant prohibition of sale, supply and use.

Current scheduling status

DMPA is not specifically scheduled in the current Poisons Standard. However, the related substances alkylamines (group entry), 1,3-dimethylamylamine (DMAA) and 1,3-dimethylbutylamine (DMBA) are in the current Poisons Standard as follows:

Alkylamines with stimulant properties

Schedule 10

ALKYLAMINES WITH STIMULANT PROPERTIES **except** when separately specified in these schedules.

Index

ALKYLAMINES WITH STIMULANT PROPERTIES

cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisooheptane, DMHA, 1,5-dimethylhexylamine, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane citrate (AMP citrate)

Schedule 10

1,3-dimethylamylamine (DMAA)

Schedule 10

1,3-DIMETHYLAMYLAMINE (DMAA).

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1,3-DIMETHYLAMYLAMINE

cross reference: 4-METHYLHEXANE-2-AMINE, DMAA

Schedule 10

1,3-dimethylbutylamine (DMBA)

Schedule 10

1,3-DIMETHYLBUTYLAMINE (DMBA) **except** when separately specified in these schedules.

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1,3-DIMETHYLBUTYLAMINE (DMBA)

cross reference: octodrine, 1-aminoisooheptane, DMHA, 1,5-dimethylhexylamine, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane Citrate (AMP Citrate)

Schedule 10

Scheduling history

DMPA has not been previously considered for scheduling; therefore, a scheduling history is not available.

DMAA

In August 2012, the ACMS considered a delegate-initiated proposal to list DMAA in Schedule 9 of the Poisons Standard following New Zealand's temporary Class Drug Notice of 8 March 2012 advising that DMAA would be classified as a temporary class drug (equivalent to Schedule 9). New Zealand's temporary prohibition of DMAA came into effect on 9 April 2012.

The ACMS noted that there was inadequate evidence to suggest DMAA's toxicological and pharmacological properties to warrant a Schedule 9 listing. DMAA was not listed in either Schedule IV to the *United Nations Convention on Narcotic Drugs, 1961* or in Schedule 1 of the *United Nations Convention on Psychotropic Substances, 1971*. There was a lack of supporting evidence to reach the conclusion that DMAA needs the same level of control as amphetamine. At the time, DMAA's

toxicological properties met the Appendix C (now Schedule 10) scheduling criteria. The Committee recommended that DMAA be placed in Appendix C (now Schedule 10) as a result of:

- The absence of an accepted therapeutic use;
- The stimulant effect that can induce a psychoactive effect;
- Its active promotion as a party drug and as a sports supplement;
- The lack of evidence of dependence;
- The significant number of adverse events including cardiac, nervous and psychiatric disorders that have been reported with use of DMAA including cerebral haemorrhage and heart attacks; and
- The high potential for misuse and abuse.

Based on DMAA's toxicity, lack of data supporting long-term safety, wide variability in potency of different doses of DMAA and the high risk of use, misuse and illicit use, the Delegate agreed with the Committee and placed DMAA in Schedule 10 effective on 8 August 2012.⁵

DMBA and alkylamines

In June 2017, following a recommendation from the ACMS, the Delegate made a final decision to create new entries for DMBA and other alkylamines with stimulant properties including 1,5-dimethylhexylamine (DMHA) in Schedule 10. The decision was based on the structural similarity of DMBA with DMAA, which was previously included in Schedule 10 of the Poisons Standard. DMBA was readily available in Australia, despite lack of proof of efficacy and safety and accepted therapeutic use. DMBA is also listed by the Australian Sports Anti-doping Authority (ASADA) and the World Anti-Doping Authority (WADA). WADA considers DMBA to be a health risk due to little pharmacological data of its effects in humans and as it is a non-approved drug. The potential for misuse and abuse was considered high.

Australian regulations

- DMPA is not listed on the [TGA Ingredient Database](#).
- There are no medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#)¹ that contain DMPA as an active ingredient.
- DMPA is not permitted to be included in listed medicines as it is not included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 2 of 2019](#)⁶.
- The [Database of Adverse Event Notifications \(DAEN\)](#)⁷ contains no reports of adverse events for products containing DMPA as an active ingredient.
- There are no products containing DMPA listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#)⁸.

International regulations

- The [European Chemicals Agency \(ECHA\)](#) hazard classification for DMPA is, 'Danger! According to the classification provided by companies to ECHA in CLP notifications this substance causes severe skin burns and eye damage and is a flammable liquid and vapour'.
- DMPA is prohibited from sport under the World Anti-Doping Agency (WADA) List of Prohibited Substances and Methods due to its structural similarity to DMAA under category 'S6: Stimulants'.
- As DMPA is an analogue of DMAA, the regulatory status of DMAA in other jurisdictions is relevant to the scheduling application. DMAA has been banned by regulatory agencies in United States of America (USA), United Kingdom, the Netherlands and Brazil because of its links to negative health events including, strokes, heart failure and sudden death.

⁵ <https://www.tga.gov.au/scheduling-decision-final/scheduling-delegates-final-decisions-dmaa-august-2012>

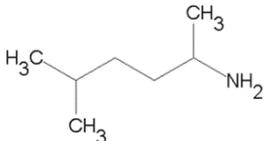
⁶ <https://www.legislation.gov.au/Details/F2019L00834>

⁷ <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

⁸ <https://portal.apvma.gov.au/pubcris>

Substance summary

Table 1: Chemical information for 1,4-dimethylpentylamine

Property	1,4-dimethylpentylamine
Chemical structure	
Molecular formula	C ₇ H ₁₇ N
Molecular weight	115.22 g/mol
CAS name	2-Amino-5-methylhexane
CAS number	28292-43-5
IUPAC and/or common and/or other names	2-hexanamine, 5-methyl-pentylamine, 1,4-dimethyl-; 1,4-dimethylamylamine; 5-methyl-2-hexylamine

Summary of pre-meeting public submissions

Two (2) submissions were received in response to [the notice published under regulation 42ZCZK advising of the proposed amendment](#). Both were in support of the proposed amendment.

The main points in support of the proposed amendment were:

- It was noted that DMPA is currently under Schedule 10 due to its similarities to 1,3-dimethylamylamine (DMAA) and 1,3-dimethylbutylamine (DMBA). The new entry is proposed to remove any ambiguity about the scheduling of this substance.
- DMPA is prohibited by the World Anti-Doping Agency (WADA) as a stimulant.
- There has been an increase in calls to the NSW Poisons Information Centre (PIC) regarding exposures to weight-loss and body-building products in the past 5 years and most of these calls required medical attention (57%).

Year	Calls to NSW PIC on body building/weight-loss products
2014	57
2015	66
2016	68
2017	79
2018	59
Jan-April 2019	30

- There is often little detail of the contents of such supplements but they commonly show signs of stimulant toxicity.
- Entry of this agent in Schedule 10 will minimise opportunity of it being included in weight loss and body building products.

Summary of ACMS advice/recommendations to the Delegate

The Committee recommended that a Schedule 10 entry for 1,4-dimethylpentylamine (DMPA) be created as follows:

Schedule 10 – New Entry

1,4-DIMETHYLPENTYLAMINE (DMPA).

Index – New Entry

1,4-DIMETHYLPENTYLAMINE (DMPA)

Schedule 10

Index – Amend Entry

ALKYLAMINES WITH STIMULANT PROPERTIES

cross reference: 1,3-dimethylbutylamine, DMBA, octodrine, 1-aminoisooheptane, DMHA, 1,5-dimethylhexylamine, 4-methylhexane-2-amine, 1,3-dimethylamylamine, DMAA, 4-amino-2-methylpentane citrate (AMP citrate), **1,4-dimethylpentylamine, DMPA.**

Schedule 10

The Committee also recommended an implementation date as soon as practicable.

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; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice included:

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

- Limited research regarding the harms and possible therapeutic benefits (DMPA has never been studied in humans, presumed to pose similar risks to safety as DMBA and DMHA)
- 1,4-dimethylpentylamine (DMPA) is covered by the Schedule 10 group entry for alkylamine with stimulant properties. It is also a structural analogue of 1,3-dimethylamylamine (DMAA) which is listed in Schedule 10 of the Poisons Standard.
- Due to its structural similarity to DMAA and its characterization as an *alkylamine with stimulant properties*, DMPA has potential for harm including stroke, heart failure and sudden death.

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

- Nil that are currently registered, use in sports supplements, the extent of which is difficult to quantify, as often products are not accurately labelled.

(c) the toxicity of a substance:

- As established for alkylamines with stimulant properties; stimulant effects can induce a psychoactive effect and adverse events have been reported with use of these.
- The potential adverse effects of alkylamines include cardiac, nervous and psychiatric disorders that have been reported with use of DMAA.
- As an analogue of DMAA, DMPA likely has similar health risks.

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

- No current registered products, or information about dosage due to a lack of human research.

(e) *the potential for abuse of a substance:*

- As established for alkylamines with stimulant properties.
- Promoted for use in sports supplements to improve athletic performance and increase weight loss.

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

- Broader issues around supplements also warrant consideration.
- Communicate for clarity that 1,4-dimethylpentylamine (DMPA) is covered by the Schedule 10 group entry for alkylamine with stimulant properties.

Delegate's considerations

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to 1,4-dimethylpentylamine;
- Advisory Committee on Medicines Scheduling's advice;
- The public submissions received before the [first closing date](#);
- Section 52E of the *Therapeutic Goods Act 1989*, in particular: (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;
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- The Australian Health Ministers' Advisory Council's [Scheduling Handbook](#) (V 1.0, January 2018).

Reasons for the interim decision

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (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.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the scheduling factors for Schedule 10.

I have made the decision to amend the current Poisons Standard by creating a new Schedule 10 entry for 1,4-dimethylpentylamine (DMPA) and I have set out my reasons below.

Although DMPA is currently captured under the Schedule 10 entry for 'alkylamines with stimulant properties' it is my view that in order to reduce potential ambiguity surrounding the scheduling status of DMPA, a separate Schedule 10 entry for DMPA is appropriate. In making my decision, I have considered that DMPA is an analogue of DMAA, it is on the World Anti-Doping Agency (WADA) list of prohibited substances and that the Early Warning Advisory (EWA) of the United Nations Office on Drugs and Crime (UNODC) categorises DMPA as a stimulant, based on its structural similarity to other known substances.

In making my decision, I considered the scheduling factors for inclusion in Schedule 10, particularly *'the substance poses such a high public health risk, including potential risk, that its sale, supply and/or use require very strict control, with access generally being prohibited'*. It is my view that DMPA meets the scheduling factors of Schedule 10 as the supply of DMPA to humans poses a risk due to the lack of appropriate trials in humans, lack of data on dosage and the potential for use for its psychoactive (stimulant) properties. I consider these factors to pose a significant public health risk so as to warrant prohibition by scheduling.

1.3. Interim decision in relation to sanguinarine

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to sanguinarine as follows:

Schedule 10 – New Entry

SANGUINARIA CANADENSIS (bloodroot) in preparations for human use except in preparations containing 0.01 per cent or less of SANGUINARINE.

INDEX – New Entry

SANGUINARIA CANADENSIS (bloodroot)

Schedule 10

SANGUINARINE

cross reference: **SANGUINARIA CANADENSIS (bloodroot)**

Proposed date of effect of the proposed amendment

1 February 2020

Reasons for the interim decision (including findings on material questions of fact)

Applicant's scheduling proposal and reasons for the proposal

An application to create a Schedule 10 entry for sanguinarine was considered.

The Applicant's proposed amendments to the Poisons Standard were:

Schedule 10 – New Entry

SANGUINARINE for therapeutic use except in preparations containing 0.1 per cent or less.

Index – New Entry

SANGUINARINE

Schedule 10

The Applicant's main points provided in support of the proposed amendments were as follows:

- *Sanguinaria canadensis* (also known as 'bloodroot') is a key ingredient of black salve. Sanguinarine derived from the root of *S. canadensis* and is purported as a treatment for cancer, including skin cancer.
- Sanguinarine leads to the indiscriminate death of normal and cancerous cells and results in extensive tissue necrosis and the formation of a thick black scab (eschar) which eventually sloughs off, leaving an open wound.
- Multiple case studies have shown that sanguinarine is not selective for tumour cells and that extensive tissue damage can result as well as a recurrence or metastasis of skin cancer.
- Sanguinarine has the potential to cause epidemic dropsy, a severe form of oedema that results from ingesting sanguinarine.
- Sanguinarine is in two listed medicines on the ARTG as components of *S. Canadensis* and in six listed medicines, one complementary medicine and one export only medicine as a component of *Chelidonium majus*.
- There has never been a published controlled clinical trial conducted in black salve's 160-year history of clinical use.

Current scheduling status

Sanguinarine is not specifically scheduled in the current Poisons Standard and has not been previously considered for scheduling. Therefore, a scheduling history is not available.

Australian regulations

Sanguinarine is currently not scheduled. However, it is an active alkaloid found in the plant species *S. canadensis* and *C. majus*.

- According to the [TGA Ingredient Database](#), *S. canadensis* is available for use as an active ingredient in: export only, listed medicines, over the counter and prescription medicines. *S. canadensis* is also available for use in listed medicines as a homeopathic ingredient only and as an excipient ingredient in prescription medicines. It is not available as an equivalent ingredient in any application.
- According to the [TGA Ingredient Database](#), *C. majus* is available for use as an active ingredient in: export only, listed medicines, over the counter and prescription medicines. *C. majus* is also available for use in listed medicines as a homeopathic ingredient only and as an excipient ingredient in prescription medicines and listed medicines. It is not available as an equivalent ingredient in any application.
- There are two (2) listed medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#)⁹ that contain *S. canadensis* as an active homeopathic ingredient. These include two non-prescription medicines:
 - XXXXXXXX – oral uncoated tablet, listed medicine for temporary relief of osteoarthritic pain. Contains *S. canadensis* (*Homeopathic*) – 450 micrograms; and
 - XXXXXXXX – oral liquid, listed medicine for temporary relief of dry cough/nasal congestion. *S. canadensis* (*Homeopathic*) 1 microlitre/mL (1:1000 dilution therefore 0.1% concentration).
- There are six (6) listed medicines, one (1) complementary medicine and one (1) export only medicine containing *C. majus* on the ARTG
- The current [Therapeutic Goods \(Permissible Ingredients\) Determination No. 2 of 2019](#)¹⁰ contains *S. canadensis* as follows:

Item	Ingredient name	Purpose	Specific requirements
4398	SANGUINARIA CANADENSIS	Homeopathic preparation ingredient (H) – an ingredient that is a constituent of a homeopathic preparation	Only for use as an active homeopathic ingredient. The potency must be more than 4X.

- The current [Therapeutic Goods \(Permissible Ingredients\) Determination No. 2 of 2019](#)¹¹ contains *C. majus* (4387) as follows:

Item	Ingredient name	Purpose	Specific requirements
1305	CHELIDONIUM MAJUS	Active ingredient (A) – a medicine that has the same meaning as in the Regulations.	When for oral or sublingual use, the medicine requires the following warning

⁹ <https://www.tga.gov.au/artg>

¹⁰ <https://www.legislation.gov.au/Details/F2019L00834>

¹¹ <https://www.legislation.gov.au/Details/F2019L00834>

		Excipient (E) – a medicine that means an ingredient that is not an active ingredient or a homoeopathic preparation ingredient. Homoeopathic preparation ingredient (H) – an ingredient that is a constituent of a homoeopathic preparation	statement on the medicine label: (CELAND) 'WARNING: Greater Celandine may harm the liver in some people. Use only under the supervision of a healthcare professional'.
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- The [Database of Adverse Event Notifications \(DAEN\)](#)¹² contains no reports of adverse events for products containing sanguinarine or the plant *S. canadensis* as an active ingredient in products that are listed on the ARTG. There are nine (9) reports of adverse events between 01/01/1971 – 21/02/2019 for ARTG products containing *C. majus*, with eight (8) as a single suspected medicine and no reported deaths.
- As at June 2012, [the TGA](#)¹³ has received four notifications of adverse events involving the use of products described as 'black salve', 'red salve' or 'cansema'. Each of these reports describes damage to the skin, subcutaneous tissue and, in one case, muscle following the application of these products. Three of the reported cases required medical intervention or follow up and in two of the cases significant scarring resulted.
- There are no products containing sanguinarine listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#).¹⁴
- The [Medicines Advisory Statement Specification 2019 \(RASML No. 5\)](#)¹⁵ does not include warning statements pertaining to sanguinarine to be included on the labelling.

International regulations

- The [European Chemicals Agency \(ECHA\)](#) has stated for sanguinarine, '*According to the majority of notifications provided by companies to ECHA in CLP notifications no hazards have been classified*'.
- The United States Food and Drug Administration (U.S. FDA) has issued warnings regarding 'scams' involving black salves. In 2009 (lasted updated 27/09/2018), the U.S. FDA website posted a warning regarding how black salves are '[offered with the false promise of drawing cancer out from the skin, but they are potentially corrosive to tissues](#)'.
- It does not appear that sanguinarine is regulated in the European regulations. However, there are two (2) regulation entries for a rhizome/root extract of the plant *Sanguinaria Canadensis* – CAS number 84929-48-6. The uses described in the European regulation include cleansing, refreshing, skin conditioning and tonic functions. There are no identified ingredients or substances listed for the two entries.
- In December 2013, [Medsafe New Zealand published a safety alert on 'black salve'](#) as part of the Trans-Tasman Early Warning System. In this publication, the Medsafe website states the black salves that are available in New Zealand are unregulated products.

¹² <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

¹³ <https://www.tga.gov.au/community-qa/black-salve-red-salve-and-cansema>

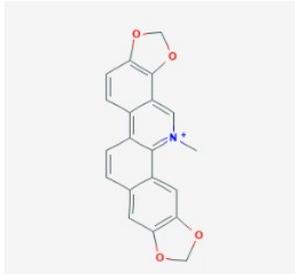
¹⁴ <https://portal.apvma.gov.au/pubcris>

¹⁵ <https://www.tga.gov.au/publication/required-advisory-statements-medicine-labels-rasml>

Substance summary

Sanguinarine is a benzylisoquinoline alkaloid and isoquinoline derivative that has strong escharotic properties.

Table 1: Chemical information for sanguinarine

Property	Sanguinarine
Chemical structure	
Molecular formula	C ₂₀ H ₁₄ NO ₄
Molecular weight	332.335 g/mol
CAS name	Sanguinarine
CAS number	2447-54-3
IUPAC and/or common and/or other names	IUPAC: 13-Methyl[1,3]benzodioxolo[5,6-c][1,3]dioxolo[4,5-i]phenanthridin-13-ium Other: [1,3]Benzodioxolo[5,6-c]-1,3-dioxolo[4,5-i]phenanthridinium, C ₂₀ H ₁₄ NO ₄ 13-methyl-, Pseudochelerythrine,, sanguinarin,, sangvinarin.

Summary of pre-meeting public submissions

Nine (9) public submissions were received in response to [the notice published under regulation 42ZCZK advising of the proposed amendment](#). Four (4) submissions were in support, three (3) that opposed and two (2) that provided general comments to the proposed amendments.

The main points in support of the proposed amendment were:

- Doctors have reported serious harms to their patients from the use of sanguinarine and consider it is a noxious and dangerous product.
- There are websites marketing black salves with claims of curing skin cancer, amongst other cancer types, which have not been scientifically tested. This presents a significant risk to self-treating patients, particularly those with low health literacy or those more vulnerable to this type of information.
- There are a number of cases documented in the literature where the use of black salve has had detrimental outcomes for patients, including:
‘The tumour appeared initially to disappear but recurred several years later requiring extensive surgery. The patient later developed metastasis (secondary growth), residual tumour found on biopsy although it appeared initially to have gone, severe scarring’.
- An article by Cliff Rosendahl titled ‘Science or Snake Oil, what is black salve?’ concluded:
‘In the future laboratory studies and ethical clinical trials might discover a beneficial role for blood-root products. But at present the use of black salve has no justifiable place in medical practice’.

- All exposures to sanguinarine or black salve reported to the NSW Poisons Information Centre (PIC) have resulted in significant tissue damage and required management in hospital. The NSW PIC have received four (4) calls in the past four (4) years, two (2) of these were errors where veterinary black salve was used instead of ichthammol ointment and two (2) were self-treatment alternative therapy for skin cancers.
- This highly toxic substance has high risk of accidental and intentional exposures which will always result in the need for hospital management. Restricting its access will reduce both of these risks.
- Although there are a number of *in vitro* studies demonstrating the apoptotic and anti-proliferative effects of sanguinarine, clinical evidence for its efficiency as a treatment for skin cancer is lacking. Similarly, the risks and full side effect profile of its use in humans have not been determined.

The main points in opposition of the proposed amendment were:

- Adding sanguinarine to Schedule 10 may have the impact of automatically restricting these herbal medicines, depending upon the exact concentration of sanguinarine in finished preparations.
- *S. canaensis* could be limited by its route of administration and/or dosage form to restrict topical use. This can be implemented at the time of listing or application for registration.
- May unintentionally and needlessly restrict other herbal medicines currently available in Australia.
- *Chelidonium majus* is an approved herbal ingredient in Australia for use in listed and registered medicines (seven separate complementary medicines). This herbal ingredient is known to contain a range of benzylisoquinoline alkaloids including chelidonine, chelerythrine, coptisine, berberine, stylophine, sanguinarine and others at a total quantity of between 0.1-1% in the dried aerial parts. It is theoretically possible for the sanguinarine content in a preparation containing *C. majus* to exceed the proposed limit of 0.1%.
- *Chelidonium majus* is an ingredient of a registered medicine on the ARTG, specifically XXXXXXXX (XXXXXXX). The efficacy and safety of XXXXXXXX have been proven in extensive preclinical studies (including long-term studies), randomized double-blind clinical studies, non-interventional studies, cohort studies and surveys of more than 50,000 patients and in the treatment of more than 80 million people since the product was launched.
- Despite the presence of sanguinarine, there is no evidence of *Chelidonium majus* being used in the production of black salve and no suggestion that it might be.
- *Eschscholzia californica* (also an approved herbal ingredient in Australia) contains between 0.5-1.2% total alkaloids including eschscholtzine, eschscholtzidine, californidine, norargemonine, bisnorargemonine, laurotetamine, protopine, chelidonine, chelerythrine, and sanguinarine (amongst others). The European Medicines Agency (EMA) states that 'no major safety concerns can be derived in relation to the use of *E. californica* in the recommended posology and conditions of use'.
- A search of the ARTG database shows that *Eschscholzia californica* is found in an additional 13 products, and *Chelidonium majus* in another 7 products. This is not including herbal liquid extracts and dry herbal material for extemporaneous dispensing by herbalists and naturopaths.
- *S. canadensis* (but not the isolated sanguinarine) is included as an ingredient in two products (ARTG numbers XXXXXXX and XXXXXXX). However, both products are homeopathic oral preparations and are not recommended for topical use in the treatment of skin cancers.
- Such consultation should consider how to effectively limit this inappropriate usage but simultaneously avoid unnecessary restriction of other safe and valuable herbal medicines containing sanguinarine.
- The upper content limit of sanguinarine of 0.1% would render *S. canadensis* and potentially other herbs such as *Chelidonium majus*, a completely restricted substance, irrespective of plant part, route of administration and professional use.

- *S. Canadensis* is available and supplied as a liquid extract for extemporaneous compounding. These are not required to be listed, but are required to be manufactured under good manufacturing practice (GMP) conditions.
- Like many plant constituents, there is significant natural variability and sanguinarine content is dependent on harvesting time, ranging between 2.81-3.96% in the dried rhizome.
- The TGA should pursue those companies and individuals manufacturing, supplying and importing medicines into Australia that are not registered on the ARTG. There are sufficient provisions that allow for this under section 19B of the *Therapeutic Goods Act 1989*.
- The TGA should review a series of products marketed and sold as black salve, analysing the actual composition of these preparations. Once this is known, a sense of the risk posed by these products will be easier to calculate, and targeted and appropriate regulatory action can be taken.
- Use the Permissible Ingredient Determination to mandate any label warning statements for products containing *S. canadensis* that the Committee finds appropriate.
- A raw material which contained sanguinarine above the Schedule 10 cut-off could not be imported, could not be sold to a finished product manufacturer and could not be used in the (legitimate) manufacture of therapeutic goods.
- Should the ACMS find the scheduling of sanguinarine necessary, it is recommended that preparations containing less than 2% of sanguinarine only be appropriate by prescription and otherwise available for use in herbal medicine preparations.

General comments to the proposed amendment were:

- There are concerns about the potential unintended impacts that the proposal may have on existing therapeutic goods and their ingredients. Feedback received indicates that the current finished products included on the ARTG are unlikely to be impacted by the proposed Schedule 10 entry for sanguinarine. However, there are concerns regarding the raw materials used to produce these products, or in relation to other herbal species.
- A raw material that contained sanguinarine above the Schedule 10 cut-off could not be imported, could not be sold to a finished product manufacturer and could not be used in the (legitimate) manufacture of therapeutic goods.
- The content of alkaloids in the chelidonium extract used is monitored regularly and the average is well under the proposed limit of 0.1% for the Schedule 10 entry.

Summary of ACMS advice/recommendations to the Delegate

The Committee recommended that a new Schedule 10 entry for sanguinarine be created as follows:

Schedule 10 – New Entry

SANGUINARIA CANADENSIS (bloodroot) in preparations for human use except in preparations containing 0.01 per cent or less of SANGUINARINE.

INDEX – New Entry

SANGUINARIA CANADENSIS (bloodroot)

Schedule 10

The Committee also recommended an implementation date as soon as practicable.

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 included:

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

- Purported benefits of black salve containing *Sanguinaria canadensis* (bloodroot) in the management serious conditions including skin cancer have not been substantiated.
- Evidence that application of black salve containing bloodroot can lead to serious damage to the skin requiring medical treatment.
- Evidence that attempted management of skin cancer with black salve containing bloodroot can lead to a delay in patients seeking proven management.
- Sanguinarine is 50% of the benzophenanthridine alkaloid content in *Sanguinaria canadensis*. While sanguinarine is present in other herbal ingredients its percentage of all benzophenanthridine alkaloid content is much lower.
- There is evidence that *Sanguinaria canadensis* in combination with zinc chloride has can have harmful effects in that its use can lead to indiscriminate death of normal and cancerous cells and may not eradicate tumour cells and therefore lead to recurrence and metastasis.

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

- Black salve containing sanguinarine is promoted for the management of skin cancer. Whilst use appears to be limited its characteristics as a natural product are likely to appeal to sections of the community.
- Sanguinarine is an alkaloid contained in many herbal products and the up scheduling request relates to one herbal product (*Sanguinaria canadensis*) when combined with another product (zinc chloride). The use of this combination is evident when considering information from the internet and from adverse event reports.

(c) the toxicity of a substance:

- Potential to cause significant damage to the skin including hypertrophic and keloid scarring (possibly requiring scar revision surgery), granulomatous plaque formation (possibly requiring topical steroid treatment) and abnormal pigmentation changes (that may require biopsy).

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

- Bloodroot is formulated as a paste/ointment when used topically for skin cancer.
- Oral forms available.

(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

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to sanguinarine;
- Advisory Committee on Medicines Scheduling's advice;
- The public submissions received before the [first closing date](#);
- Section 52E of the *Therapeutic Goods Act 1989*, in particular: (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 Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- The Australian Health Ministers' Advisory Council's [Scheduling Handbook](#) (V 1.0, January 2018).

Reasons for the interim decision

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (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; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the scheduling factors for Schedule 10.

I have made the decision to amend the current Poisons Standard by creating a new Schedule 10 entry for sanguinarine and I have set out my reasons below.

Having considered the SPF 2018, it is my view that sanguinarine meets the Schedule 10 scheduling factors. In making a recommendation for a Schedule 10 entry, I have taken into account the potential for sanguinarine to cause significant harm to members of the public who are seeking to use a product that they believe to be natural and therefore safe. I consider the critical risk to public health to be the escharotic properties of black salve containing sanguinarine, particularly when used for self-treatment of skin cancers. This can lead to a delay in patients seeking proven management. In assessing these risks, I have considered that there is a lack of evidence to support the use of black salve in the treatment of skin cancers, together with documented adverse events including severe scarring, tumour recurrence and metastasis.

In my deliberations, I considered that sanguinarine itself may not pose significant risk and that there is a lack of toxicity data to support this. I took into account the arguments made in the public submissions in opposition to the scheduling of sanguinarine including, but not limited to, the impact the scheduling decision may have on herbal products. In particular, the concern that the specific scheduling of sanguinarine may inadvertently capture other plant species that contain this substance. In considering these factors and the advice obtained from the Committee, it is my view that the best way to mitigate these concerns is to limit the sanguinarine content in *Sanguinaria canadensis* to 0.01 per cent so it is in line with the permitted ingredient determination for homeopathic use, thereby not impacting other ingredients that may contain sanguinarine. I consider that the new scheduling entry for *Sanguinaria canadensis* will allow for the continued use of this plant in homeopathic products, whilst simultaneously prohibiting its use in black salve preparations.

1.4. Interim decision in relation to finasteride

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision not to amend the current Poisons Standard in relation to finasteride.

Reasons for the interim decision (including findings on material questions of fact)

Applicant's scheduling proposal and reasons for the proposal

An application to amend the Schedule 4 entry for finasteride was considered.

The Applicant's proposed amendments to the Poisons Standard were:

Schedule 4 – Amend Entry

FINASTERIDE for human therapeutic use, **except** when included in Schedule 3.

Schedule 3 – New Entry

FINASTERIDE for use in males with androgenetic alopecia (male pattern hair loss) in preparations containing not more than 1 mg per dose unit in packs not greater than 30 dosage units.

Appendix H – New Entry

FINASTERIDE

Index – Amend Entry

FINASTERIDE

Schedule 4

Schedule 3

Appendix H

The Applicant's main points provided in support of the proposed amendments were as follows:

- Finasteride fulfils the criteria for a Schedule 3 substance and will provide an alternative to topical minoxidil for consumers.
- Consumers can easily identify the symptoms of male pattern hair loss and it can quite easily be verified by the pharmacist to ensure that there is no other reason for the hair loss.
- The product has been on the market for a number of years and pharmacists are well equipped to provide advice to consumers on the adverse effects, interactions and contraindications (in particular, the potential risk to the male foetus if finasteride is handled by pregnant women).
- The risk profile of the medicine is well defined and there are no identified drug interactions of clinical significance.
- There is little risk of misuse, abuse or illicit use as it does not have any effect outside of its use in hair loss or in larger doses for benign prostatic hyperplasia (BPH).

Current scheduling status

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

Schedule 4

FINASTERIDE.

Index

FINASTERIDE

Schedule 4

Scheduling history

In November 1993, finasteride was first considered for scheduling by the National Health and Medical Research Council's, Drugs and Poisons Schedule Standing Committee (DPSSC). The Committee noted that at its 166th meeting, the Australian Drug Evaluation Committee (ADEC) had recommended approval for the registration of finasteride tablets (XXXXXXXXXXXX) for the treatment and control of symptomatic BPH in patients who were not candidates for immediate surgery. The Committee agreed that finasteride be included in Schedule 4 of the Poisons Standard.

In May 1998, the Drugs and Poisons Schedule Committee (DPSC) considered information from the 195th ADEC Minutes from February 1998 relating to a new strength finasteride tablet indicated for the treatment of male pattern hair loss (androgenic alopecia) to increase hair growth and prevent hair loss in men aged 18 years or older. The Committee agreed that the existing Schedule 4 classification was appropriate.

In October 2007, finasteride was again considered at the meeting of the National Drugs and Poisons Schedule Committee (NDPSC) for potential inclusion in Appendix D. In May 2007, the National Co-ordinating Committee on Therapeutic Goods identified inconsistencies between the Poisons Standard's Appendix D and Australian Drug Evaluation Committee (ADEC) 'Prescribing Medicines in Pregnancy' booklet with respect to Category X medicines (i.e. medicines that have a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or where there is a possibility of pregnancy). The Committee noted that there was the possibility of off-label use in women for an unapproved indication, although it would only be prescribed by specialist endocrinologists who would be aware of the pregnancy contraindication. However, due to its specialist indication, that it would only be prescribed by a specialist and that there was adequate warning that it was not for use in women, the Committee agreed that finasteride was suitable to remain in Schedule 4 only and did not warrant inclusion in Appendix D.

Australian regulations

- According to the [TGA Ingredient Database](#), finasteride is available for use as an active ingredient in biologicals, export only and prescription medicines and as an excipient in biologicals, devices and prescription medicines. It is not available as an equivalent ingredient in any application.
- There are 29 medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#)¹⁶ that contain finasteride as an active ingredient. All 29 products are prescription medicines, containing finasteride at either 1 mg (13 products) or 5 mg (16 products).
- Finasteride is indicated for the treatment and control of symptomatic BPH in patients who were not candidates for immediate surgery and for the treatment of male pattern hair loss (androgenic alopecia) to increase hair growth and prevent hair loss in men aged 18 years or older.
- Finasteride is not permitted to be included in listed medicines as it is not included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 2 of 2019](#)¹⁷.
- The [Database of Adverse Event Notifications \(DAEN\)](#)¹⁸ contains 222 reports of adverse events for products containing finasteride as an active ingredient, with 203 reports where finasteride was the single suspected medicine. There was one report of death associated with finasteride use.
- There are no products containing finasteride listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#)¹⁹.

International regulations

- Finasteride is included in the [Canadian Food and Drug Regulations](#) as a restricted drug.

¹⁶ <https://www.tga.gov.au/artg>

¹⁷ <https://www.legislation.gov.au/Details/F2019L00834>

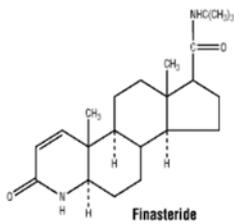
¹⁸ <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

¹⁹ <https://portal.apvma.gov.au/pubcris>

- The [European Chemicals Agency \(ECHA\)](#) hazard classification for finasteride is, 'Danger... This substance is very toxic to aquatic life with long lasting effects, may damage fertility or the unborn child, causes damage to organs through prolonged or repeated exposure, is harmful if swallowed and is suspected of damaging fertility or the unborn child'.
- In the United States and New Zealand, finasteride is available as a prescription medicine.

Substance summary

Table 1: Chemical information for finasteride

Property	Finasteride
Chemical structure	 <p style="text-align: center;">Finasteride</p>
Molecular formula	C ₂₃ H ₃₆ N ₂ O ₂
Molecular weight	372.55 g/mol
Chemical name	<i>N</i> -(1,1-dimethylethyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide.
CAS number	98319-26-7
IUPAC and/or common and/or other names	(1S,3aS,3bS,5aR,9aR,9bS,11aS)- <i>N</i> -tert-butyl-9a,11a-dimethyl-7-oxo-1,2,3,3a,3b,4,5,5a,6,9b,10,11-dodecahydroindeno[5,4-f]quinoline-1-carboxamide.

Toxicity

In clinical studies, single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for three months did not result in side effects. No specific treatment is recommended for over dosage with finasteride. Finasteride is contraindicated for use in women when they are or may potentially be pregnant. Type II 5α-reductase inhibitors have the ability to inhibit conversion of testosterone to dihydrotestosterone (DHT) in some tissues and as a result, these drugs, including finasteride, may cause abnormalities of the external genitalia of a male foetus when administered to a pregnant woman. Women who are or may potentially be pregnant should not handle crushed or broken tablets of finasteride or handle tablets with wet hands, because of the possibility of absorption of finasteride and the subsequent potential risk to a male foetus. Whole tablets are coated to prevent contact with the active ingredient during normal handling.

Pharmacology: mechanism of action

Finasteride is a competitive and specific inhibitor of type II 5α-reductase with which it slowly forms a stable enzyme complex. Turnover from this complex is extremely slow (t_{1/2} ~ 30 days). Finasteride has no affinity for the androgen receptor and has no androgenic, anti-androgenic, oestrogenic, anti-oestrogenic or progestational effects. Inhibition of this enzyme blocks the peripheral conversion of testosterone to the androgen DHT, resulting in significant decreases in serum and tissue DHT concentrations. Finasteride produces a rapid reduction in serum DHT concentrations, reaching significant suppression within 24 hours of dosing. Hair follicles contain type II 5α-reductase. In men with male pattern hair loss, the balding scalp contains miniaturised hair follicles and increased amounts of DHT and administration of finasteride decreases scalp and serum DHT concentrations in these men. In addition, men with a genetic deficiency of type II 5α-reductase do not suffer from male

pattern hair loss. These data and the results of the clinical studies confirm that finasteride inhibits the process responsible for miniaturisation of the scalp hair follicles, leading to reversal of the balding process.

Summary of pre-meeting public submissions

Seven (7) public submissions were received in response to [the notice published under regulation 42ZCZK advising of the proposed amendment](#). One (1) submission was in support, five (5) were opposed and one (1) that provided general comments to the proposed amendment.

The main points in support of the proposed amendment were:

- Finasteride 1 mg meets the scheduling factors for Schedule 3 (Pharmacist Only Medicines).
- Finasteride for androgenetic alopecia would be expected to be used long term. Therefore, it is believed that the pack size for Schedule 3 supply should allow at least one months' supply to adequately support and improve access for patients.
- In view of the safety profile of finasteride 1 mg oral preparations, and to support optimal treatment options for androgenetic alopecia in men, it is appropriate to include finasteride in Appendix H of the Poisons Standard.
- In order to ensure appropriate and safe use of Schedule 3 finasteride, issues will need to be considered and information, guidance and practice support provided to pharmacists, including:
 - Current therapy;
 - Age;
 - Informed choice;
 - Understanding how finasteride might help;
 - Establishing reasonable treatment expectations;
 - Storage and handling of finasteride tablets;
 - Monitoring ongoing treatment;
 - Clarification regarding the existence of 5 mg finasteride which will continue to be a Prescription Only medicine with a different approved indication; and
 - Practice advice around recording or labelling requirements and uploading of information in the patients my health record.
- Specific consideration is warranted on whether an upper limit on age should be stipulated for Schedule 3 use given the range of published information regarding age-related efficacy.

The main points in opposition of the proposed amendment:

- The current Schedule 4 entry for finasteride remains appropriate due to the potential serious health risks associated with the substance, which requires a healthcare professional intervention.
- The ability to differentiate the diagnosis of androgenetic alopecia from other forms of scalp alopecia is not easily made by a non-clinician.
- Down-scheduling introduces a risk of inadequate communication to the patient of known safety issues, most notably those related to the effect of finasteride on the serum prostate-specific antigen (PSA) test and the potential for mechanism-based teratogenic effects of finasteride on a developing male foetus if a pregnant women is exposed to the drug.
- Given the controversy around PSA as a marker for prostate cancer, medical management of this and other potential side-effects is essential as well as taking other conditions or co-morbidities into account.

- Potential safety risks associated with finasteride need to be clearly communicated as they significantly outweigh the cosmetic benefits. This is especially important as long term/continued use of the medicine is recommended to obtain maximum benefit.
- It is well documented that when administered to a pregnant woman, finasteride may cause abnormalities of the external genitalia of a male foetus. Therefore, it is contraindicated for women who are or may potentially be pregnant.
- While finasteride is not indicated for women, there is potential for the substance to be misused or for women to be accidentally exposed to it.
- Androgenetic alopecia is common among men and women, and therefore, may not be clear for consumers that the medicine is only indicated for men and that women should not be exposed to it whatsoever.
- Females with androgenetic alopecia could potentially use the product after it is obtained by a male, especially if the product is also advertised directly to consumers.
- Finasteride is classified as a prescription medicine in the United States (U.S.) and European market.
- In recent years, the U.S. Food and Drug Administration (FDA) have included additional safety/risk statements to strengthen the warning labels for finasteride products. New safety information about the increased risk of being diagnosed with a more serious form of prostate cancer (high-grade prostate cancer) was introduced. Similar warnings were added into the Australian product information in 2013.
- In 2012, the U.S. FDA announced that product labels for finasteride 1mg require warnings for libido disorders, ejaculation disorders and orgasm disorders that continued after discontinuation of the drug.
- There is potential for finasteride to be misused if it is included in Appendix H. As androgenetic alopecia is common among men and women, from an advertising perspective, the dangers of using finasteride in women will not be clear, especially in a 15 or 30 second commercial.
- It is likely that the convenience of a tablet will influence consumers who currently use topically applied minoxidil over the counter products to switch to finasteride 1mg tablets. It may actually cause confusion that can lead the consumer to believe that they have the similar safety profile. The similarity in indication between the two medications might increase the possibility of women incorrectly acquiring finasteride 1mg for self-use if it became available as a Pharmacist Only Medicine.
- There is potential for finasteride misuse by adolescents who could acquire this drug for self-use from a third party if it were to become available as a Pharmacist Only Medicine.
- Post Finasteride Syndrome (PFS) – is a disease that has been reported to occur in some male patients who have taken finasteride. Reports of symptoms include sexual, physical and neurological symptoms that may persist after the patient has stopped taking finasteride
- Rescheduling finasteride to Schedule 3 could expose pharmacists to a significant risk of litigation should it be prescribed incorrectly. This would be difficult for pharmacists to defend in the absence of a documented full consultation.
- The above issues cannot be discussed over the counter at a pharmacy. Pharmacists are not adequately trained to discuss these issues.
- The treatment of hair loss is a highly lucrative and easily abused industry. People seeking help are often highly motivated to find a ‘cure’ and are easily exploited.

General comments on the proposed amendment:

- Speculation regarding the plausibility of PFS due to the referencing low-quality studies and skewed public discussion. The stance is taken that PFS is a condition not recognised by the scientific community.

- It was questioned that PFS is something that is not based on clinical evidence and may well be an example of mass hysteria by a group of patients who have been self-selected to suffer from this 'debilitating' condition.
- It was also questioned that if PFS was real that the TGA should have already removed finasteride containing products from the ARTG. Due to it not being removed, it would suggest that it is a safe and an efficacious medicine.
- Finasteride does not produce significant side effects in terms of sexual function.

Summary of ACMS advice/recommendations to the Delegate

The Committee recommended that the scheduling of finasteride 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; and (e) the potential for abuse of a substance.

The reasons for the advice included:

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

- The risks are already covered by inclusion in Schedule 4.
- Can mask the diagnosis of more serious conditions.

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

- Therapeutic use for hair loss.

(c) the toxicity of a substance:

- Covered under Schedule 4 entry.
- Does not meet Schedule 3 Scheduling Factors because of issues around PSA, uncertainty surrounding post finasteride syndrome and it is a known teratogen.

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

- Nil.

(e) the potential for abuse of a substance:

- Potential for inappropriate use.

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

- Nil.

Delegate's considerations

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to finasteride;
- Advisory Committee on Medicines Scheduling's advice;
- The public submissions received before the [first closing date](#);
- Section 52E of the *Therapeutic Goods Act 1989*, in particular: (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 (e) the potential for abuse of a substance;
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- The Australian Health Ministers' Advisory Council's [Scheduling Handbook](#) (V 1.0, January 2018).

Reasons for the interim decision

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (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; and (e) the potential for abuse of a substance.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the scheduling factors for Schedule 4 and Schedule 3.

I have made a decision that the scheduling of finasteride remains appropriate under Schedule 4 and I have set out my reasons below.

I am not persuaded by the evidence supplied by the Applicant that there is a public health benefit of down scheduling finasteride to Schedule 3. Whilst the Applicant argues that finasteride 1 mg meets the scheduling factors for Schedule 3, I am not satisfied that these factors would result in a public health benefit that would outweigh my concern that finasteride is a Category X medication. I note there are currently no Category X substances in Schedule 3.

I have considered that there is potential for inappropriate use of finasteride and significant safety issues. In particular, finasteride does not have a well-defined risk profile and can cause irreversible health effects such as the development of breast and prostate cancer and teratogenic effects on a developing male foetus if pregnant women are exposed to the drug. I am not convinced that if finasteride were to be a Schedule 3 substance that a pharmacist would ensure that Prostate-Specific Antigen (PSA) levels are checked before dispensing the medication. I am of the view that this may result in undetected prostate cancer and a delay in seeking treatment.

I have also considered that there is the possibility that finasteride use may result in Post Finasteride Syndrome. However, I note that at present there is limited evidence to support this. On balance, whilst a Schedule 3 status may increase the use of finasteride and provide pharmacists more opportunities to utilise their training, I find there is little benefit to public health and significant risks associated with easing access restrictions to enable cosmetic use. I note also that the majority of public submissions were against the down scheduling of finasteride to Schedule 3.

In considering these factors and the advice obtained from the Committee, I am of the view that down scheduling finasteride to Schedule 3 would set a dangerous precedent for Category X medications, and the potential risks from broader access under Schedule 3 significantly outweigh the benefits.

2 Interim decisions on proposed amendments referred to the Advisory Committee on Chemicals Scheduling (ACCS #25, June 2019)

2.1. Interim decision in relation to lambda-cyhalothrin

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision not to amend the current Poisons Standard in relation to lambda-cyhalothrin.

Reasons for the interim decision (including findings on material questions of fact)

Applicant's scheduling proposal and reasons for the proposal

An application to amend the current Poisons Standard with respect to lambda-cyhalothrin was considered. The application proposed to amend the cut-off for lambda-cyhalothrin in Schedule 5 from 2.5 per cent to 4 per cent in aqueous preparations of microencapsulated lambda-cyhalothrin.

The Applicant's proposed amendments to the Poisons Standard were:

Schedule 5 – Amend Entry

LAMBDA-CYHALOTHRIN:

- a) in aqueous preparations containing 1 per cent or less of lambda-cyhalothrin; or
- b) in aqueous preparations containing ~~2.5~~4 per cent or less of microencapsulated lambda-cyhalothrin.

The Applicant's main points provided in support of the proposed amendment were as follows:

- The acute toxicity of the formulated product meets the criteria stipulated in the Scheduling Policy Framework, with the exception of the estimated acute oral toxicity, which was determined based on the up-and-down method.
- The Australian Pesticides and Veterinary Medicines Authority (APVMA) recently evaluated acute toxicity data for a product containing approximately 3.5% lambda-cyhalothrin.
- The formulated product had low toxicity via the oral, dermal and inhalation routes of exposure:
 - Oral LD₅₀ in rats was estimated to be 1750 mg/kg bw using the up-and-down method;
 - Dermal LD₅₀ in rats was >5000 mg/kg bw; and
 - Inhalation LC₅₀ in rats was >2520 mg/m³ (nose-only; maximum attainable concentration).
- The primary eye irritation study with the formulated product revealed slight irritation that resolved completely by 48 hours following administration of the test material.
- The primary skin irritation study with the formulated product revealed slight irritation that resolved completely by 7 days following administration of the test material.
- The product did not induce a sensitisation response when tested according to the Buehler method.

Current scheduling status

Lambda-cyhalothrin is currently listed in the Poisons Standard as follows:

Schedule 7

LAMBDA-CYHALOTHRIN **except** when included in Schedule 5 or 6.

Schedule 6

LAMBDA-CYHALOTHRIN:

- a) in aqueous preparations containing 25 per cent or less of microencapsulated lambda-cyhalothrin; or
- b) in emulsifiable granule formulations containing 25 per cent or less lambda-cyhalothrin; or
- c) in other preparations containing 1.6 per cent or less of lambda-cyhalothrin

except when included in Schedule 5.

Schedule 5

LAMBDA-CYHALOTHRIN:

- a) in aqueous preparations containing 1 per cent or less of lambda-cyhalothrin; or
- b) in aqueous preparations containing 2.5 per cent or less of microencapsulated lambda-cyhalothrin.

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LAMBDA-CYHALOTHRIN

Schedule 7

Schedule 6

Schedule 5

Scheduling history

In November 1987, the Drugs and Poisons Schedule Committee (DPSC) decided to include first aid and safety directions for lambda-cyhalothrin.

In August 1990, the DPSC decided to include preparations containing 1 per cent or less of lambda-cyhalothrin in Schedule 6 and all other preparations containing lambda-cyhalothrin in Schedule 7, based on the toxicity profile of lambda-cyhalothrin. Toxicity data discussed at this meeting included a one year oral dosing study in dogs, which revealed be short-lived and non-cumulative dose related neurotoxic effects. In addition, a study in human volunteers devoid of asthma revealed that aerosols of lambda-cyhalothrin elicited some mild reaction in more than 50 per cent of volunteers. A dose response relationship was established for the incidences of smarting and watering of the eyes, sneezing, blocked or runny noses and throat/lung irritation.

In November 1991, the DPSC decided to include aqueous preparations containing 1 per cent or less of lambda-cyhalothrin in Schedule 5. The reason for this decision was that the water-based product containing 1 per cent or less of lambda-cyhalothrin provided it was confined to use by pest control operators through a registration mechanism. It is noted in the minutes that the oral LD₅₀ for the product in rats was >2000 mg/kg.

In November 1994, the National Drugs and Poisons Schedule Committee (NDPSC) considered toxicological data on a microencapsulated aqueous suspensions containing 10 per cent lambda-cyhalothrin. Members noted that technical lambda-cyhalothrin had been demonstrated to have slight skin and eye irritancy and may cause transitory facial numbness in humans. The Committee agreed that because of the potential for moderate skin irritation and temporary facial numbness, and the restriction of its use to professional pest operators that microencapsulated aqueous suspensions containing 2.5 per cent or less of lambda-cyhalothrin be included in Schedule 5.

In August 1999, the NDPSC decided to include microencapsulated preparations containing 25 per cent or less of lambda-cyhalothrin in Schedule 6.

In August 2014, the chemicals scheduling delegate decided to increase the allowed concentration in Schedule 6 from 1.5 to 1.6 per cent to ensure that the product formulation, when expressed in grams per 100 millilitre (as per Part I of the Poisons Standard), is covered by the amended entry.

In October 2017, ACCS recommended, and the chemicals scheduling delegate agreed to amend the Schedule 6 entry for lambda-cyhalothrin to include emulsifiable granule formulations containing 25 per cent or less of lambda-cyhalothrin.

Australian regulations

- Lambda-cyhalothrin is not listed on the [TGA Ingredient Database](#).
- Lambda-cyhalothrin is not permitted to be included in listed medicines as it is not included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 2 of 2019](#)²⁰.
- There is one adverse report relating to lambda-cyhalothrin in the APVMA's [Adverse Experience Reporting Program annual reports](#)²¹ from 1995-2015. The 2015 report included one (1) case of malaise, allergy and respiratory problems.
- As of 7 May 2019, the [Database of Adverse Event Notifications \(DAEN\)](#)²² contains no reports of adverse events for products containing lambda-cyhalothrin as an active ingredient.
- As of 7 May 2019, there are 53 products containing lambda-cyhalothrin listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#)²³. Of these, 14 are active constituent listings and 39 are end-use products.

International regulations

United States (US)

Lambda-cyhalothrin was registered with the US Environmental Protection Agency (US EPA) in 1989 and is registered as a biochemical/conventional chemical. It is a restricted use, broad spectrum insecticide used to control most major aphid, caterpillar and beetle pests on a wide variety of crops and for public health pests such as mosquitoes and cockroaches in non-agricultural settings.

Canada

Lambda-cyhalothrin is a registered pesticide with Health Canada.

UK

Lambda-cyhalothrin was first approved for use in the UK in 1988 (Advisory Committee on Pesticides, 1988).

EU

Lambda-cyhalothrin is currently a registered product with the European Chemicals Agency (ECHA). The [ECHA](#) hazard classification for lambda-cyhalothrin is, '*Danger! According to the classification provided by companies to ECHA in CLP notifications this substance is fatal if inhaled, is very toxic to aquatic life with long lasting effects, is toxic if swallowed, is toxic in contact with skin and is very toxic to aquatic life*'.

New Zealand

Lambda-cyhalothrin is currently a registered product.

Substance summary

Lambda-cyhalothrin is a synthetic pyrethroid insecticide which contains only two (1*R cis Z-S* and 1*S cis Z-R*) of cyhalothrin's four possible stereoisomers. Lambda-cyhalothrin insecticidal activity is believed to be through interference with sodium channels in the nervous system of insects, leading to paralysis and, eventually, death.

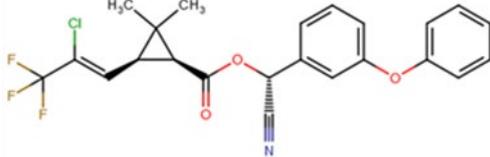
²⁰ <https://www.legislation.gov.au/Details/F2019L00834>

²¹ <https://apvma.gov.au/node/10946>

²² <https://apps.tga.gov.au/Prod/daen/daen-entry.aspx>

²³ <https://portal.apvma.gov.au/pubcris>

Table 1: Chemical information for lambda-cyhalothrin

Property	Lambda-cyhalothrin
Chemical structure	
Molecular formula	C ₂₃ H ₁₉ ClF ₃ NO ₃
Molecular weight	449.85 g/mol
CAS name	(R)-cyano(3-phenoxyphenyl)methyl (1S,3S)-rel-3-[(1Z)-2-chloro-3,3,3-trifluoro-1-propen-1-yl]-2,2-dimethylcyclopropanecarboxylate
CAS number	91465-08-6
IUPAC and/or common and/or other names	3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyano(3-phenoxyphenyl)methyl cyclopropane carboxylate (IUPAC)

Summary of pre-meeting public submissions

No public submissions were received in response to the proposed amendment.

Summary of ACCS advice/recommendations to the Delegate

The Committee recommended that the scheduling of lambda-cyhalothrin 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 included:

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

- Risks:
 - Product may be supplied in the domestic market, acute toxicity primarily neurotoxicity but we do not have detailed data on the nature of the toxic outcomes.
- Benefits:
 - Used as a broad band insecticide.
 - Effective insecticide with a long history of use.

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

- Product to be used by professionals only as an insecticide but it is used in commercial, industrial, domestic and public spaces.

(c) the toxicity of a substance:

- Formulated product: Acute oral toxicity LD₅₀ 1750 mg/kg bw.
- 4 hr inhalational LC₅₀ = 2520 mg/m³ max attainable concentration.

- Main route of exposure is dermal and inhalational.
- Oral toxicity may be within Schedule 6 parameters for aqueous preparations of up to 4% microencapsulated lambda-cyhalothrin.
- Acute oral toxicity is imprecise and the Committee are not confident in a down-scheduling or a change to the cut-off.

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

- Supplied as a concentrate in 250mL and 5L containers. Aqueous preparation of microencapsulated lambda-cyhalothrin.
- Applied by hand held equipment.
- Potential for backpack application.
- Potential use in domestic settings.

(e) the potential for abuse of a substance:

- Potential use by non-professionals.

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

- Nil.

Delegate's considerations

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to lambda-cyhalothrin;
- Advisory Committee on Chemicals Scheduling's advice;
- Section 52E of the *Therapeutic Goods Act 1989*, in particular: (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 Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- The Australian Health Ministers' Advisory Council's [Scheduling Handbook](#) (V 1.0, January 2018).

Reasons for interim decision

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (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.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the scheduling factors for Schedule 5.

I have made the decision not to amend the Schedule 5 entry for lambda-cyhalothrin in the Poisons Standard and I have set out my reasons below.

I have taken into account the toxicological data provided by the Applicant and I am not persuaded that the acute oral LD₅₀ toxicity data can be reliably interpreted to justify a Schedule 5 entry. I consider the results from acute oral toxicity study that used the OECD Test Guideline (425) 'up and down' method for deriving the acute oral LD₅₀ with a surrogate formulation containing approximately 4% w/v lambda-cyhalothrin, to be imprecise. As there was a death of one of the laboratory animals at 1750 mg/kg bw, the data does not provide confidence that the acute oral LD₅₀ value can be extrapolated to a value greater than 2000 mg/kg bw as suggested by the Applicant. I am of the opinion that the data in this instance cannot be extrapolated in order to support a change to the scheduling cut-off for lambda-cyhalothrin.

I have also taken into account the potential for products containing lambda-cyhalothrin to be used in the domestic setting. The product is intended for professional use. However, it is possible that it may be used in domestic settings by non-professionals as the smallest proposed pack size is 250 mL. I acknowledge that domestic users can still buy a product containing lambda-cyhalothrin if it is in Schedule 6, but the signal heading "POISON" rather than "CAUTION" is considered more appropriate in maintaining public health given the proposed product's toxicity profile that is consistent with criteria listed in the SPF (2018).

2.2. Interim decision in relation to sarolaner

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to sarolaner as follows:

Schedule 6

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

Schedule 5 – Amend Entry

SAROLANER **for veterinary use in divided preparations each** containing 120 mg or less of sarolaner per dosage unit.

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SAROLANER

Schedule 6
Schedule 5

Proposed date of effect of the proposed amendment

1 February 2020

Reasons for the interim decision (including findings on material questions of fact)

Applicant's scheduling proposal and reasons for the proposal

An application to amend the current Poisons Standard with respect to sarolaner was considered. The application proposed to amend the current Schedule 5 entry for sarolaner to include topical veterinary medicines.

The Applicant's proposed amendments to the Poisons Standard were:

Schedule 5 –Amend Entry

SAROLANER **in veterinary preparations** for the treatment, prevention and control of fleas and ticks in dogs in oral divided preparations each containing 120 mg or less of sarolaner per dosage unit.

The Applicant's main points provided in support of the proposed amendment were as follows:

- The spot-on product line, XXXXXX, containing 60 mg/mL selamectin plus 10 mg/mL sarolaner, has a significantly reduced acute oral toxicity to sarolaner *per se* which, together with other acute toxicity endpoints for sarolaner, does not meet the Scheduling Policy Framework (SPF)²⁴ criteria for Schedule 6.
- Sarolaner is in Schedule 6 of the Poisons Standard due to its moderate oral toxicity (LD₅₀ = 783 mg/kg bw (rats), point estimate).
- Sarolaner oral preparations containing 120 mg or less sarolaner are in Schedule 5 due to the lower content of sarolaner (4 per cent w/w) and reduced oral toxicity of the product.
- Gastro-intestinal absorption of sarolaner in cats and dogs is >85 per cent versus <55 per cent via skin absorption. Skin absorption in humans is likely to be significantly lower (estimated at <15 per cent by APVMA).
- A topical preparation containing 10 mg or less of sarolaner will therefore present a lower hazard from accidental/incidental ingestion than an oral preparation containing 120 mg or less sarolaner.

²⁴ <https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>

- Child-resistant packaging will reduce the risks of a child accidentally ingesting the product.
- Risks to veterinarians and adult public users of XXXXXX (containing 60 mg selamectin and 10 mg sarolaner in a 1 mL tube – max pack size) have been assessed by APVMA as negligible.
- Risks to veterinarians and the public (adults and children) from handling cats treated with the maximum recommended dose of sarolaner (2 mg/kg bw) have been similarly assessed by APVMA as negligible.
- XXXXXX meets the health & safety criteria in Section 5A of the *Agricultural and Veterinary Chemicals Code Act* (1994).²⁵ In addition, APVMA considers that XXXXXX meets APVMA guidelines (Toxicology, part 3, sections 5.6) for safe use as a domestic product.
- The acute oral (and dermal) LD₅₀ of XXXXXX is >2000 mg/kg bw.²⁶ This is similar to the LD₅₀ for sarolaner chews for dogs containing 120 mg or less sarolaner (XXXXX) and to other isoxazoline substances (including afoxolaner, fluralaner and lotilaner), with similar toxicity and use profiles, which are all included in Schedule 5 of the Poisons Standard.
- Currently, although XXXXXX for cats containing sarolaner at 10 mg/mL meets the SPF scheduling factors for inclusion in Schedule 5, topical preparations are excluded by virtue of the specificity of the Schedule 5 entry for sarolaner (i.e. for oral preparations in dogs).

Current scheduling status

Sarolaner is currently listed in Schedules 5 and 6 of the Poisons Standard as follows:

Schedule 6

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

Schedule 5

SAROLANER for the treatment, prevention and control of fleas and ticks in dogs in oral divided preparations each containing 120 mg or less of sarolaner per dosage unit.

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SAROLANER

Schedule 6

Schedule 5

Other members of the isoxazoline class, afoxolaner, fluralaner and lotilaner, are in the Poisons Standard as follows:

Schedule 5

AFOXOLANER in oral divided preparations each containing 150 mg or less of afoxolaner per dosage unit

- a) for the treatment and prevention of flea infestations and control of ticks in dogs; or
- b) for the treatment and prevention of flea infestations, control of ticks, gastrointestinal nematodes and heartworm in dogs, when combined with milbemycin oxime.

FLURALANER.

LOTILANER.

²⁵ <https://www.legislation.gov.au/Details/C2016C00999>

²⁶ Equivalent to approximately 25 mg/kg bw sarolaner.

Scheduling history

On 17 March 2016, the Delegate made a delegate-only decision following consideration of an Applicant's proposal for a new Schedule 5 entry for sarolaner. The Delegate confirmed the interim decision to schedule sarolaner in Schedule 6 with a cut-off to Schedule 5 for the treatment, prevention and control of fleas and ticks in dogs in oral divided preparations each containing 120 mg or less of sarolaner per dosage unit. The reasons for the Schedule 6 entry were due to the acute toxicity profile of the substance, which met the SPF factors for Schedule 6. However, the acute poisoning risk to humans of proposed products containing 120 mg sarolaner was considered to be low, and as a result, the Delegate agreed to a 120 mg cut-off to Schedule 5. This was consistent with the Schedule 5 listing of other ectoparasiticides.

Australian regulations

- Sarolaner is not listed on the [TGA Ingredient Database](#).
- Sarolaner is not used in human medicines. As of 7 May 2019, there are no medicines on the [Australian Register of Therapeutic Goods \(ARTG\)](#)²⁷ that contain sarolaner as an active ingredient.
- Sarolaner is not permitted to be included in listed medicines as it is not included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 2 of 2019](#)²⁸.
- As of May 2019, the [Database of Adverse Event Notifications \(DAEN\)](#)²⁹ contains no reports of adverse events for products containing sarolaner as an active ingredient.
- On the 13 March 2019, there are seven (7) products containing sarolaner listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#)³⁰. Six (6) of these veterinary medicine products are registered as Schedule 5 parasiticides for dogs (as chewable tablets) and one (1) is approved as an active constituent containing sarolaner.
- Sarolaner is an APVMA approved active constituent.

International regulations

- The [European Chemicals Agency \(ECHA\)](#) hazard classification for sarolaner is, 'Warning! According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life with long lasting effects and is harmful if swallowed'.
- Sarolaner has been considered by the [European Medicines Agency's Committee for Medicinal Products for Veterinary Use \(CVMP\)](#),³¹ which has recommended the granting of a marketing authorisation for veterinary medicinal product XXXXXX, containing sarolaner at up to 120 mg per chewable tablet. On 21 February 2019, the CVMP recommended the granting of a marketing authorisation for veterinary medicinal product, XXXXXXXX, intended for use in cats (EMA/V/C/005093, 2019).
- XXXXXX (selamectin & sarolaner) has been approved in the EU (EMA/V/C/004194, 2016), Japan (2018) and New Zealand (A011536, 2018) and is currently under evaluation in Australia, Brazil, Canada, China and the USA.

²⁷ <https://www.tga.gov.au/artg>

²⁸ <https://www.legislation.gov.au/Details/F2019L00834>

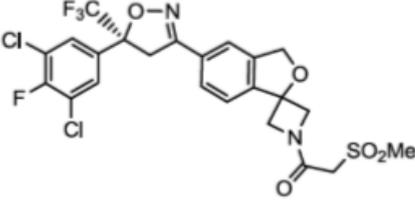
²⁹ <https://apps.tga.gov.au/PROD/DAEN/daen-entry.aspx>

³⁰ <https://portal.apvma.gov.au/pubcris>

³¹ <https://www.ema.europa.eu/en/committees/committee-medicinal-products-veterinary-use-cvmp>

Substance summary

Table 1: Chemical information for sarolaner

Property	Sarolaner
Chemical structure	 The chemical structure of Sarolaner is a spiro compound. It consists of a 3,5-dichloro-4-fluorophenyl ring attached to a 5-(trifluoromethyl)-4,5-dihydro-1,2-oxazol-3-yl ring. This oxazole ring is spiro-fused to an azetidinium ring. The azetidinium ring is further substituted with a methanesulfonyl group (-SO ₂ Me).
Molecular formula	C ₂₃ H ₁₈ C ₁₂ F ₄ N ₂ O ₅ S
Molecular weight	581.36 g/mol
CAS name	Sarolaner
CAS number	1398609-39-6
IUPAC and/or common and/or other names	Ethanone, 1-[5'-[(5S)-5-(3,5-dichloro-4-fluorophenyl)-5(trifluoromethyl)-4,5-dihydro-1,2-oxazol-3-yl]-3'H]-spiro[azetidinium3,1'-[2]benzofuran]-1-yl]-2-methanesulfonylethan-1-one. PF-6450567

Summary of pre-meeting public submissions

No public submissions were received in response to the proposed amendment.

Summary of ACCS advice/recommendations to the Delegate

The Committee recommended that the Schedule 5 entry for sarolaner be amended as follows:

Schedule 5 – Amend Entry

SAROLANER for veterinary use in divided preparations each containing 120 mg or less of sarolaner per dosage unit.

The Committee also recommended an implementation date of 1 February 2020.

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; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the advice included:

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

- Benefits:
 - Benefits for companion animals and owners.
- Risks:
 - Risk controlled by package size and dosage.

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

- Safe use of ectoparasiticide by pet owners.

(c) *the toxicity of a substance:*

- Safety margin is sufficient to allow a lower schedule for the type of preparation under consideration i.e. Schedule 5 rather than the parent schedule for sarolaner, which is Schedule 6 due to the acute oral toxicity of the substance itself.

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

- Child resistant unit dose packaging reduces risk of accidental ingestion by a child such that a lower schedule is appropriate (Schedule 5 rather than Schedule 6).
- The Schedule 5 entry already limits the allowable dose per unit to 120 mg and the current scheduling consideration relates to a product with at most 10 mg per unit dose.

(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

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to sarolaner;
- Advisory Committee on Chemicals Scheduling's advice;
- Section 52E of the *Therapeutic Goods Act 1989*, in particular: (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 Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- The Australian Health Ministers' Advisory Council's [Scheduling Handbook](#) (V 1.0, January 2018).

Reasons for the interim decision

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (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.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the scheduling factors for Schedule 5.

I have made the decision to amend the current Poisons Standard by amending the Schedule 5 entry for sarolaner and I have set out my reasons below.

I am in agreement with the Applicant's proposal that the removal of the reference to the specific indication (i.e. 'treatment, prevention and control of fleas and ticks') in the Schedule entry is acceptable on the basis that veterinary use is unlikely to have a significant impact on the risk to human toxicity. In making my decision, I have considered that sarolaner is unlikely to be used to treat or prevent conditions other than ectoparasite infestation in animals and that the upper limit on the amount of sarolaner per dosage unit precludes use for very large animals (e.g. non-companion animal).

I consider the critical issue for human toxicity to be the amount of sarolaner which may be accidentally ingested or the amount of exposure from contact with topically applied product. I am of the opinion that limiting the maximum quantity per dosage unit and requiring the dosage form to be a 'divided preparation' will mitigate this risk through both formulation and packaging. This will also limit human exposure to a single unit at a time, either through normal use or through accidental ingestion.

I also acknowledge that the Schedule 5 listing will ensure new products are subject to regulatory approval by the APVMA. This will further mitigate public health risks by ensuring that child resistant packaging is used. I am in agreement with the Committee's advice that removal of a reference to the intended route of administration is acceptable, given the assessment considered both oral ingestion and topical application. I am satisfied that the Schedule 5 scheduling factors are met in this instance.

2.3. Interim decision in relation to broflanilide

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to broflanilide as follows:

Schedule 6 – New Entry

BROFLANILIDE except when included in Schedule 5.

Schedule 5 – New Entry

BROFLANILIDE in preparations containing 0.3 per cent or less of broflanilide.

INDEX – New Entry

BROFLANILIDE

Schedule 6

Schedule 5

Proposed date of effect of the proposed amendment

1 February 2020

Reasons for the interim decision (including findings on material questions of fact)

Applicant's scheduling proposal and reasons for the proposal

An application to amend the current Poisons Standard with respect to broflanilide was considered. The application proposed to create a new Schedule 6 entry for broflanilide, with a concentration cut-off of 3 per cent for Schedule 5.

The Applicant's proposed amendments to the Poisons Standard were:

Schedule 6 – New Entry

BROFLANILIDE, except when included in Schedule 5.

Schedule 5 – New Entry

BROFLANILIDE, in preparations containing 3 per cent or less of broflanilide.

The Applicant's main points provided in support of the proposed amendment were as follows:

- Broflanilide and its products are of low acute toxicity. While broflanilide is not genotoxic, ovarian and uterine tumours were seen in rats, with a clear dose threshold. This is consistent with a Schedule 6 entry for broflanilide, with a risk of producing irreversible harm. The proposal for a cut off at 3 per cent to Schedule 5 is a reflection of the clear thresholds resulting in products at this level, which are unlikely to produce irreversible toxicity. No specialised equipment is required for safe use, and the likelihood of injury can be mitigated through appropriate packaging and simple label warnings. Broflanilide will only be made publically available in formulated products which will be labelled appropriately.
- Broflanilide is a new meta-diamide pro-pesticide, classified as a benzamide, acting through a novel mechanism. Its active invertebrate metabolite acts as a gamma-aminobutyric acid receptor antagonist. It is effective against pests with resistance to cyclodienes and fipronil.
- The Australian Pesticides and Veterinary Medicines Authority (APVMA) has received an application for the new active constituent broflanilide and a set of products including aerosol, granular bait and bait products containing between 0.045 g/kg and 2.5 g/kg broflanilide.
- Broflanilide is of very low acute toxicity from the oral, dermal and inhalational route. It is slightly irritating to the eyes, not irritating to the skin, and is not a skin sensitiser.

- In repeat dose studies in laboratory animals, broflanilide primarily affects the adrenal glands and, in females, the ovaries.
- Broflanilide is not considered to be genotoxic. In rats, an increase in benign ovarian tumours was seen, along with an increase in uterine adenocarcinomas at high doses, which correlated with an increase of endometrial hyperplasia at lower doses. The mode of action of these tumours is likely considered to be non-genotoxic with a clear dose threshold.
- Broflanilide did not demonstrate developmental toxicity and there were no adverse effects on fertility or reproduction in multi-generation studies.
- A range of other insecticides for use as baits and for crack and crevice treatments exist, including products containing abamectin, fipronil, hydramthylnon, imidacloprid and pyriproxyfen.

Current scheduling status

Broflanilide is not specifically scheduled in the current Poisons Standard. Therefore, a scheduling history is not available.

Australian regulations

- Broflanilide is not listed on the [TGA Ingredient Database](#).
- As of 7 May 2019, broflanilide is neither an excipient nor active ingredient in any medicines on the [Australian Register of Therapeutic Goods \(ARTG\)](#)³².
- Broflanilide is not permitted to be included in listed medicines as it is not included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 2 of 2019](#)³³.
- As of 7 May 2019, the [Database of Adverse Event Notifications \(DAEN\)](#)³⁴ contains no reports of adverse events for products containing broflanilide as an active ingredient.
- As of 7 May 2019, there are no products containing broflanilide listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#)³⁵.

International regulations

- Broflanilide is not listed on the [European Chemicals Agency \(ECHA\)](#) website.
- There are no products containing broflanilide currently approved/registered in America, Canada, the European Union or New Zealand. Applications are currently under consideration in America, Canada, Mexico and India.

³² <https://www.tga.gov.au/artg>

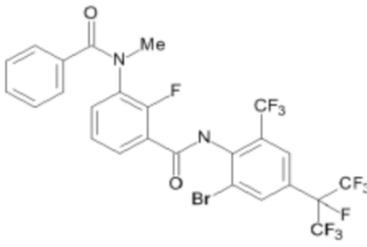
³³ <https://www.legislation.gov.au/Details/F2019L00834>

³⁴ <https://apps.tga.gov.au/PROD/DAEN/daen-entry.aspx>

³⁵ <https://portal.apvma.gov.au/pubcris>

Substance summary

Table 1: Chemical information for broflanilide

Property	Broflanilide
Chemical structure	
Molecular formula	C ₂₅ H ₁₄ BrF ₁₁ N ₂ O ₂
Molecular weight	663.28 g/mol
CAS name	3-(benzomethylamino)-N-[2-bromo-4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-6-(trifluoromethyl)phenyl]-2-fluorobenzamide
CAS number	1207727-04-5
IUPAC and/or common and/or other names	N-[2-bromo-4-(perfluoropropan-2-yl)-6-(trifluoromethyl)phenyl]-2-fluoro-3-(N-methylbenzamido)benzamide (IUPAC)

Summary of pre-meeting public submissions

No public submissions were received in response to the proposed amendment.

Summary of ACCS advice/recommendations to the Delegate

The Committee recommended that new Schedule 5 and 6 entries for broflanilide be created as follows:

Schedule 6 – New Entry

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

Schedule 5 – New Entry

BROFLANILIDE in preparations containing 0.3 per cent or less of broflanilide.

INDEX – New Entry

BROFLANILIDE

Schedule 6

Schedule 5

The Committee also recommended an implementation date of 1 February 2020.

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 included:

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

- Risks:
 - The irreversible toxicity data is consistent with a Schedule 6 listing but there is a clear threshold for these effects (ovarian and uterine tumours in rats).
- Benefits:
 - A very low concentration of broflanilide is required, resulting in low level exposure for users.
 - New pesticide active for control of insects with novel action.

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

- Pesticide for control of insects.
- Currently proposed products include domestic uses.
- Broflanilide is proposed for use in a range of products as a bait product to control insect pests, including flies, ants, termites and cockroaches in a range of indoor and outdoor situations, including domestic, commercial, industrial and agricultural patterns of use containing between 0.045 g/kg and 2.5 g/kg broflanilide.

(c) the toxicity of a substance:

- Although of low acute toxicity, the repeat dose toxicity is consistent with Schedule 6.
- Consistent with Schedule 5 at 0.3% or less – low toxicity, non-corrosive, has a low health hazard and low potential of causing harm reduced by packaging and simple warning and safety directions on the label.

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

- Products proposed for non-food producing uses contain low levels of broflanilide and low daily use rates.
- Appropriate labelling and packaging controls for these products will be assigned by the APVMA.
- A number of products are currently under consideration containing broflanilide for non-food producing use between 0.045 g/kg and 2.5 g/kg broflanilide.
- Appropriate labels, including directions for use and appropriate First Aid and Safety Directions will be approved by the APVMA.

(e) the potential for abuse of a substance:

- There are currently no reports of misuse or overdose with broflanilide.
- There is not expected to be any potential for broflanilide to be converted into a controlled substance.

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

- Nil.

Delegate's considerations

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to broflanilide;
- Advisory Committee on Chemicals Scheduling's advice;

- Section 52E of the *Therapeutic Goods Act 1989*, in particular: (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 Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- The Australian Health Ministers' Advisory Council's [Scheduling Handbook](#) (V 1.0, January 2018).

Reasons for interim decision

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (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.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the scheduling factors for Schedule 5 and Schedule 6.

I have made the decision to amend the current Poisons Standard by creating new Schedule 5 and Schedule entries for broflanilide and I have set out my reasons below.

Having considered the SPF 2018, it is my view that a parent schedule entry for broflanilide in Schedule 6 is appropriate. While broflanilide is not genotoxic, ovarian and uterine tumours were seen in rats but not mice with a clear dose threshold. This is consistent with the Schedule 6 scheduling factors that broflanilide has a moderate risk of producing irreversible harm. Further, taking the results of the carcinogenicity study in rats into account, and the fact that broflanilide is a new pesticide active acting through a novel mechanism, I am persuaded that broflanilide presents as a moderate health hazard and in accordance with the Scheduling Factors for Schedule 6.

I am satisfied that broflanilide exhibits low acute toxicity and clear thresholds which are unlikely to produce irreversible toxicity at concentrations below 0.3%. At below 0.3%, broflanilide has a low health hazard that is consistent with the Schedule 5 scheduling factors.

2.4. Interim decision in relation to trifludimoxazin

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to trifludimoxazin as follows:

Schedule 5 – New Entry

TRIFLUDIMOXAZIN **except** in preparations containing 12.5 per cent or less.

INDEX – New Entry

TRIFLUDIMOXAZIN

Schedule 5

Proposed date of effect of the proposed amendment

1 February 2020

Reasons for the interim decision (including findings on material questions of fact)

Applicant's scheduling proposal and reasons for the proposal

An application to amend the current Poisons Standard with respect to trifludimoxazin was considered. The application proposed to exempt trifludimoxazin from control by scheduling, by creating an Appendix B entry for agricultural use as a herbicide.

The Applicant's proposed amendments to the Poisons Standard were:

Appendix B, Part 3 – New Entry

SUBSTANCE	DATE OF ENTRY	REASON FOR LISTING	AREA OF USE
TRIFLUDIMOXAZIN	[TBD]	a (Low Toxicity)	1.1 (Herbicide)

The Applicant's main points provided in support of the proposed amendments were as follows:

- The toxicology profile of trifludimoxazin is well characterised. There is low acute toxicity, with no deaths or adverse clinical signs seen at the highest tested dose. The product is not intended to be used in the home garden, with intended uses limited to the agricultural sector. Due to the low toxicity, no personal protective equipment was required during use of the product.

Current scheduling status

Trifludimoxazin is not currently scheduled and has not been previously considered for scheduling.

Australian regulations

- Trifludimoxazin is not listed on the [TGA Ingredient Database](#).
- As of 7 May 2019, trifludimoxazin is neither an excipient nor active ingredient in any medicines on the [Australian Register of Therapeutic Goods \(ARTG\)](#)³⁶.
- Trifludimoxazin is not permitted to be included in listed medicines as it is not included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 2 of 2019](#)³⁷.

³⁶ <https://www.tga.gov.au/artg>

³⁷ <https://www.legislation.gov.au/Details/F2019L00834>

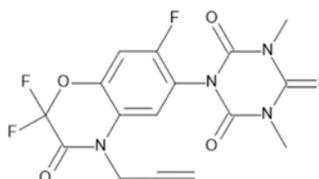
- As of 7 May 2019, the [Database of Adverse Event Notifications \(DAEN\)](#)³⁸ contains no reports of adverse events for products containing trifludimoxazin as an active ingredient.
- As of 7 May 2019, there are no products containing trifludimoxazin listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#)
- Trifludimoxazin is not a previously endorsed APVMA active constituent.

International regulations

- Trifludimoxazin is not listed on the [European Chemicals Agency \(ECHA\)](#) website.
- Trifludimoxazin has yet to be registered in any other country.

Substance summary

Table 1: Chemical information for trifludimoxazin

Property	Trifludimoxazin
Chemical structure	
Molecular formula	C ₁₆ H ₁₁ F ₃ N ₄ O ₄ S
Molecular weight	412.35 g/mol
CAS name	Dihydro-1,5-dimethyl-6-thioxo-3-[2,2,7-trifluoro-3,4-dihydro-3-oxo-4-(2-propyn-1-yl)-2H-1,4-benzoxazin-6-yl]-1,3,5-triazine-2,4(1H,3H)-dione
CAS number	1258836-72-4
IUPAC and/or common and/or other names	1,5-dimethyl-6-thioxo-3-[2,2,7-trifluoro-3-oxo-4-(prop-2-yn-1-yl)-3,4-dihydro-2H-1,4-benzoxazin-6-yl]-1,3,5-triazinane-2,4-dione (IUPAC)

Summary of pre-meeting public submissions

No public submissions were received in response to the proposed amendment.

Summary of ACCS advice/recommendations to the Delegate

The Committee recommended that a new Schedule 6 entry be created for trifludimoxazin as follows:

Schedule 6 – New Entry

TRIFLUDIMOXAZIN **except** for agricultural use in preparations containing 12.5 per cent or less.

INDEX – New Entry

TRIFLUDIMOXAZIN

Schedule 6

³⁸ <https://apps.tga.gov.au/PROD/DAEN/daen-entry.aspx>

The Committee also recommended an implementation date of 1 February 2020.

It was 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 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.

The reasons for the advice included:

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

- Risks:
 - Repeat dose exposure in animal studies cause neurotoxic effects at comparatively high doses.
 - Moderate health hazard with moderate risk of irreversible toxicity with repeated exposure.
- Benefit:
 - Agriculture benefit – pre-planting of cereal crop weed reduction. Estimates of exposure during appropriate use at 12.5% have resulted in adequate safety margins.

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

- Agricultural use only for weed reduction pre-planting.

c) the toxicity of a substance:

- Schedule 6 – Repeat dose exposure in animal studies show neurotoxic effects at comparatively high doses.
- Moderate health hazard with moderate risk of irreversible toxicity with repeated exposure. Consistent with Schedule 6.

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

- In proposed formulation and usage, substance poses low risk.

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

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to trifludimoxazin;
- Advisory Committee on Chemicals Scheduling's advice;
- Section 52E of the *Therapeutic Goods Act 1989*, in particular: (a) 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;
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- The Australian Health Ministers' Advisory Council's [Scheduling Handbook](#) (V 1.0, January 2018).

Reasons for interim decision

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (a) 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.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the scheduling factors for Schedule 5 and Schedule 6 and the considerations for amending Appendix B.

Contrary to advice provided by the Committee, I have made the decision to amend the current Poisons Standard by creating a new Schedule 5 entry for trifludimoxazin. I have set out my reasons below.

I have taken into account the toxicological data on trifludimoxazin that was provided by the Applicant and I note that the acute toxicity for all endpoints is low and does not appear to pose a risk. Based on my analysis of the available data, I consider that the adverse effects noted in repeat dose toxicity studies (neurogenerative changes and endocrine disruption) were only seen at high to very high doses after prolonged exposure. The margins of exposure for these toxicological endpoints have been calculated to be in excess of 10 to 1000-fold the proposed Acceptable Daily Intake (ADI) that has been used in establishing the dietary and Occupational Health & Safety risk assessments by the Applicant (APVMA).

When all the scheduling factors for Schedules 5 and 6 are considered as a whole, I find that trifludimoxazin to be most consistent with the scheduling factors for Schedule 5, based on its low acute toxicity, low health hazard (other than at high to very-high exposures), the potential for it to cause minor effects to humans in normal use, and that the substance has a low potential to cause harm when used with appropriate packaging and labelling. Appropriate packaging and labelling have been proposed by the pesticide regulator (APVMA) in its consideration of the approval of the substance, trifludimoxazin, and the registration of a trifludimoxazin-containing product.

I agree with the Committee's advice to include a cut-off to unscheduled at 12.5% due to the low acute toxicity seen at this concentration and the acceptable margins of exposure. I do not agree with the Committee's advice to include a specific limitation on the use of the substance for agricultural purposes in the proposed Scheduling entry. As the substance will be used in products intended for use as a preplanting herbicide in grain crops, the pesticide regulator (APVMA) has already considered its appropriate use. Should the use of the substance be expanded in the future, the pesticide regulator is the most appropriate authority to undertake a risk assessment to determine whether such use is approved.

2.5. Interim decision in relation to saflufenacil

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to saflufenacil as follows:

Schedule 7

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

Schedule 5 – Amend Entry

SAFLUFENACIL in water dispersible granules ~~preparations~~ **or a water-based suspension concentrate.**

Index

SAFLUFENACIL

Schedule 7
Schedule 5

Proposed date of effect of the proposed amendment

1 February 2020

Reasons for the interim decision (including findings on material questions of fact)

Applicant's scheduling proposal and reasons for the proposal

An application to amend the current Poisons Standard with respect to saflufenacil was considered. The application proposed to amend the current Schedule 5 entry for saflufenacil to accommodate water-based suspension concentrates (SC).

The Applicant's proposed amendments to the Poisons Standard were:

Schedule 5 – Amend Entry

SAFLUFENACIL in water dispersible granules ~~preparations~~ **or a water-based suspension concentrate.**

The Applicant's main points provided in support of the proposed amendments were as follows:

- The restriction of the current Schedule 5 entry to wettable granule formulations of saflufenacil (the only formulation proposed at the time of scheduling) was based on data from a dermal absorption study with a SC formulation conducted in rats.
- In 2011, the Scheduling Delegate and Committee concluded that the dermal absorption of saflufenacil from wettable granule formulations was very low.
- Based on the low dermal absorption of saflufenacil and substantial margins of exposure calculated for all the stipulated application methods of a wettable granule product (700 g/kg saflufenacil), together with slight skin and eye irritation for the wettable granule product, a cut-off to Schedule 5 for all water dispersible granule products containing saflufenacil was decided by the Delegate.
- The conclusions on dermal absorption for wettable granule formulations were based on a study conducted in rats with a SC formulation containing 342.2 g/L of saflufenacil.
- The product XXXXXXXXXX (also a SC formulation), contains a lower amount of saflufenacil (250 g/L of saflufenacil), has low acute oral, dermal and inhalational toxicity, is not an eye irritant or skin sensitiser and is a slight skin irritant at most.

Current scheduling status

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

Schedule 7

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

Schedule 5

SAFLUFENACIL in water dispersible granule preparations.

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SAFLUFENACIL

Schedule 7

Schedule 5

Scheduling history

In June 2009, the National Drug and Poisons scheduling Committee (NDPSC) decided to include saflufenacil in Schedule 7. The NDPSC particularly noted reports that saflufenacil increased skeletal malformations (bent scapula) in one animal species (redacted in minutes) at a relatively low dose in the absence of any significant signs of maternal toxicity. The NDPSC was concerned with the bent scapula effect, noting that this was an irreversible effect that was a highly unusual developmental toxicity marker.

In October 2009, the NDPSC considered post-meeting submissions requesting inclusion of saflufenacil in Schedule 6, which included new developmental toxicity data. The submissions claimed that the new developmental data demonstrated that there were marked interspecies differences with regard to protoporphyrin (PPO) inhibition by saflufenacil. The NDPSC noted that the study only considered saflufenacil's role in inhibiting one enzyme (protoporphyrinogen oxidase – PPO), where other PPO inhibitors had not produced the bent scapula effect. It was therefore argued that it was not possible to conclude that only this particular enzyme was responsible for the developmental toxicity effect. The NDPSC decided that the June 2009 Schedule 7 decision remained appropriate until the new data on developmental toxicity had been evaluated through the usual APVMA process.

In February 2010, the NDPSC was advised that the Applicant had updated its 2009 evaluation to include the new developmental toxicity data. The evaluator advised:

- Saflufenacil had low acute toxicity, it was a slight skin irritant and a minimal eye irritant, and had no skin sensitisation potentials. Notwithstanding its low acute toxicity, saflufenacil had shown developmental toxicity potential in XXXX (irreversible toxicity) but not in XXXXX. Consequently, the NDPSC may consider it appropriate to retain saflufenacil in Schedule 7.
- Alternatively, Schedule 6 may be more appropriate since the developmental toxicity was not seen in XXXXX, *in vitro* data indicated that saflufenacil was a PPO inhibitor and XXXXX are significantly more sensitive to this effect than rabbits and humans. However, the mode of action (MOA) for saflufenacil induced skeletal malformation had not been established, though there was limited evidence to suggest that PPO inhibition may not be relevant to the MOA.

The February 2010 NDPSC meeting confirmed the June 2009 Schedule 7 decision.

The Applicant subsequently submitted additional data to the APVMA in support of requested changes to the scheduling of their product. The Risk Assessment Technical Report on saflufenacil included a scheduling recommendation. A delegate agreed that this was a matter for a scheduling consideration and that advice from the ACCS was required.

In June 2011, the ACCS considered a proposal to reschedule saflufenacil from Schedule 7 to Schedule 6. The Delegate also sought advice on potential cut-offs from Schedule 6 to Schedule 5, including the possibility of a 70 per cent cut-off limited to water dispersible granule formulations. The Committee recommended that an exemption be created from the Schedule 7 saflufenacil parent entry to Schedule 5 for water dispersible granule preparations.

Australian regulations

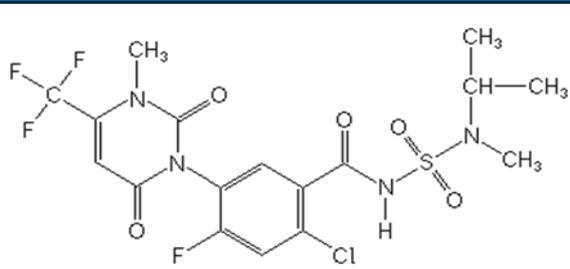
- Saflufenacil is not listed on the [TGA Ingredient Database](#).
- Saflufenacil is not used in human medicines. As of 7 May 2019, there are no medicines on the [Australian Register of Therapeutic Goods \(ARTG\)](#)³⁹ that contain saflufenacil as an active ingredient.
- Saflufenacil is not permitted to be included in listed medicines as it is not included in the [Therapeutic Goods \(Permissible Ingredients\) Determination No. 2 of 2019](#)⁴⁰.
- As of May 2019, the [Database of Adverse Event Notifications \(DAEN\)](#)⁴¹ contains no reports of adverse events for products containing saflufenacil as an active ingredient.
- Saflufenacil is an APVMA approved active constituent.
- As of 7 May 2019, there is one (1) registered product containing saflufenacil listed on the [Public Chemical Registration Information System Search \(PUBCRIS\)](#)⁴².

International regulations

- The [European Chemicals Agency \(ECHA\)](#) hazard classification for saflufenacil is, 'Warning! According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life and is very toxic to aquatic life with long lasting effects'.
- Saflufenacil is approved for use in the United States, Canada and New Zealand.
- Saflufenacil is not approved for use in the European Union.

Substance summary

Table 1: Chemical information for saflufenacil

Property	Saflufenacil
Chemical structure	
Molecular formula	C ₁₇ H ₁₇ ClF ₄ N ₄ O ₅ S
Molecular weight	500.85 g/mol
CAS name	2-chloro-5-[3,6-dihydro-3-methyl-2,6-dioxo-4-(trifluoromethyl)-1(2H)-pyrimidinyl]-4-fluoro-N-[[methyl(1-methylethyl)amino]sulfonyl]benzamide
CAS number	372137-35-4
IUPAC and/or common and/or other names	N'-[2-chloro-4-fluoro-5-(3-methyl-2,6-dioxo-4-(trifluoromethyl)-3,6-dihydro-1(2H)-pyrimidinyl)benzoyl]-N-isopropyl-N-methylsulfamide (IUPAC)

³⁹ <https://www.tga.gov.au/artg>

⁴⁰ <https://www.legislation.gov.au/Details/F2019L00834>

⁴¹ <https://apps.tga.gov.au/PROD/DAEN/daen-entry.aspx>

⁴² <https://portal.apvma.gov.au/pubcris>

Summary of pre-meeting public submissions

No public submissions were received in response to the proposed amendment.

Summary of ACCS advice/recommendations to the Delegate

The Committee recommended amending the Schedule 5 entry for saflufenacil in the Poisons Standard as follows:

Schedule 5 – Amend Entry

SAFLUFENACIL in water dispersible granules ~~preparations~~ or a water-based suspension concentrate.

The Committee also recommended an implementation date of 1 February 2020.

It was 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; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice included:

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

- The scheduling recommendation is consistent with the 2011 scheduling decision for Schedule 5 inclusion of water based suspension.
- Benefits:
 - Allowing a new product formulation.

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

- Nil.

c) *the toxicity of a substance:*

- Nil.

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:

- The Committee suggests APVMA reconsiders safety directions in light of the pregnancy warnings.

Delegate's considerations

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to saflufenacil;
- Advisory Committee on Chemicals Scheduling's advice;
- Section 52E of the *Therapeutic Goods Act 1989*, in particular: (a) risks and benefits of the use of a substance; and (f) any other matters that the Secretary considers necessary to protect public health;
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and

- The Australian Health Ministers' Advisory Council's [Scheduling Handbook](#) (V 1.0, January 2018).

Reasons for interim decision

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (a) risks and benefits of the use of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the scheduling factors for Schedule 5.

I have made the decision to amend the current Poisons Standard by amending the Schedule 5 entry for saflufenacil and I have set out my reasons below.

I have taken into account the toxicological data on the substance provided by the Applicant and I am of the opinion that amending the Schedule 5 entry to include use in water-based suspension concentrates will not present an increased risk to public health. In making this decision, I have considered that the current Schedule 5 entry for water dispersible granules was made on the basis of low dermal absorption and that the study supporting this decision was conducted using a suspension concentrate formulation of a higher concentration. I acknowledge that saflufenacil has the potential to cause developmental toxicity. However, as no new data have been presented since the last scheduling decision in 2011, I consider the risk of the suspension concentrate formulation to be equivalent to that of the water dispersible granule formulation.

I agree with the Committee's recommendation that the toxicity data for saflufenacil is consistent with the scheduling factors for Schedule 5 on the grounds that the assessed product has low acute oral, dermal and inhalational toxicity, it is not an eye irritant or skin sensitiser and it is at most a slight skin irritant. I find that the substance has a low potential for causing harm and any potential harm is reduced through the use of appropriate packaging with simple warnings and safety directions on the label.

3 Interim decision on proposed amendment referred to the Advisory Committee on Medicines and Chemicals Scheduling in joint session (Joint ACCS/ACMS # 22, June 2019)

3.1. Interim decision in relation to arbutin

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision to amend the current Poisons Standard in relation to arbutin as follows:

Schedule 4 – New Entry

ARBUTIN **except** in oral herbal preparations containing 500 mg or less of arbutin per recommended daily dose.

INDEX – Amend Entry

ARBUTIN

cross-reference: HYDROQUINONE

Schedule 4

Index – Amend Entry

HYDROQUINONE

cross reference: ARBUTIN, GLYCOSYLATED HYDROQUINONE, MONOBENZONE

Schedule 6

Schedule 4

Schedule 2

Proposed date of effect of the proposed amendment

1 June 2020

Reasons for the interim decision (including findings on material questions of fact)

Applicant's scheduling proposal and reasons for the proposal

An application to amend the Poisons Standard with respect to arbutin was considered.

The Applicant's proposed amendments to the Poisons Standard were:

Schedule 4 – New Entry

ARBUTIN in preparations for human therapeutic or cosmetic use **except**:

- a) when included in Schedule 2; or
- b) in hair preparations containing 0.75 per cent; or
- c) in cosmetic nail preparations containing 0.05 per cent; or
- d) in oral herbal preparations containing 500mg or less of arbutin per recommended daily dose.

Schedule 2 – New Entry

ARBUTIN in preparations for human external therapeutic or cosmetic use containing 5 per cent or less of arbutin **except**:

- a) in hair preparations containing 0.75 per cent; or
- b) in cosmetic nail preparations containing 0.05 per cent.

Index – Amend Entry

ARBUTIN

cross reference: HYDROQUINONE

Schedule 4

Schedule 2

Additional proposed amendment to the hydroquinone index entry as follows:

Index – Amend Entry

HYDROQUINONE

cross reference: ARBUTIN, GLYCOSYLATED HYDROQUINONE, MONOBENZONE

Schedule 6

Schedule 4

Schedule 2

The Applicant's main points provided in support of the proposed amendments were as follows:

- Commonplace and frequent population exposure to arbutin and hydroquinone via common dietary components at levels equal to likely levels arising from herbal exposure, combined with a lack of reports of adverse or toxic effects linked to naturally occurring arbutin, provides an established history of safety;
- Available evidence shows that almost all hydroquinone released upon ingestion of arbutin is rapidly conjugated and eliminated with the urine;
- Available evidence shows that the quantity of free, unconjugated hydroquinone released from arbutin *in vivo* is two orders of magnitude lower than the European Medicines Agency's (EMA) permitted daily exposure (PDE) level for hydroquinone; and
- Naturally occurring arbutin in herbal medicines therefore does not present an unacceptable risk to human health.

Current scheduling status

Arbutin is not specifically scheduled in the Poisons Standard but has a cross reference to hydroquinone in the index of the Poisons Standard as follows:

Index

ARBUTIN

cross reference: HYDROQUINONE

Hydroquinone is listed in the Poisons Standard as follows:

Schedule 6

HYDROQUINONE **except:**

- a) when included in Schedule 2 or 4; or
- b) in preparations containing 10 per cent or less of hydroquinone.

Schedule 4

HYDROQUINONE (other than its alkyl ethers separately specified in this Schedule) in preparations for human therapeutic or cosmetic use **except:**

- a) when included in Schedule 2; or
- b) in hair preparations containing 0.3 per cent or less of hydroquinone; or
- c) in cosmetic nail preparations containing 0.02 per cent or less of hydroquinone.

Schedule 2

HYDROQUINONE (excluding monobenzene and alkyl ethers of hydroquinone included in Schedule 4) in preparations for human external therapeutic or cosmetic use containing 2 per cent or less of hydroquinone **except**:

- a) in hair preparations containing 0.3 per cent or less of hydroquinone; or
- b) in cosmetic nail preparations containing 0.02 per cent or less of hydroquinone.

Hydroquinone is also included in Appendix E and F as follows:

Appendix E, Part 2

HYDROQUINONE	First Aid Instructions
When included in Schedule 2	A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once).)
When included in Schedule 4 or 6	A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once), G2 (If swallowed, give activated charcoal if instructed. (Note – the words ‘at once’ to be added to instruction A), G3 (If swallowed, do NOT induce vomiting.), E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes), R2 (If swallowed or inhaled, remove from contaminated area. Apply artificial respiration if not breathing. Do not give direct mouth-to-mouth resuscitation. To protect rescuer, use air-viva, oxy-viva or one-way mask. Resuscitate in a well-ventilated area), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water)

Appendix F, Part 3

HYDROQUINONE	WARNING STATEMENTS	SAFETY DIRECTIONS
When in Schedule 2	45 (WARNING – If a pigmented spot or mole has recently become darker, changed colour, become enlarged or itchy, or bleeds, do not use this product, see your doctor immediately. Do not use on children. Do not use near the eyes. Mild irritation may occur; stop use if it becomes severe. If fading is not evident in three months, seek doctor’s advice)	
except when in Schedule 2 or 4.	-	1 (Avoid contact with eyes),4 (Avoid contact with skin)

Index

HYDROQUINONE

cross reference: ARBUTIN, GLYCOSYLATED HYDROQUINONE, MONOBENZONE

Schedule 6

Schedule 4

Schedule 2

Scheduling history

Hydroquinone

In 1969, hydroquinone was first included in Schedule 4 by the Poisons Schedule Sub-Committee (PSSC). This listing was due to concerns raised about the promotion and free availability of skin lightening creams which were being targeted to the PNG and Indigenous Australian populations.

In February 1971, the PSSC agreed to amend the Schedule 4 entry for hydroquinone to allow an exemption from scheduling for preparations of hydroquinone containing ≤ 2 per cent.

In May 1986, the Drugs and Poisons Schedule Committee (DPSC) considered deleting the ≤ 2 per cent exemption i.e. all human use hydroquinone and monobenzene becoming Schedule 4. The DPSC considered the overall Adverse Drug Reactions Advisory Committee (ADRAC) profile for hydroquinone and monobenzene and recommended that these substances warranted a Schedule 4 listing. However, this recommendation was not implemented.

In May 1987, the DPSC agreed to foreshadow creation of a new Schedule 2 entry for hydroquinone for human therapeutic or cosmetic use at ≤ 2 per cent (with an Appendix F Warning Statement). This was confirmed at the July 1987 Meeting.

In June 2008, the National Drugs and Poison Schedule Committee (NDPSC), following a request from the Over the Counter (OTC) Medicines Section of the TGA, gave consideration as to whether hydroquinone was appropriately scheduled. The NDPSC noted concerns about possible carcinogenicity of hydroquinone with prolonged usage.

In October 2008, the NDPSC foreshadowed consideration of the rescheduling of hydroquinone and possible up-scheduling hydroquinone in preparations for human external use (excluding hair dyes) to Schedule 3.

In August 2018, the TGA outlined changes that would be made to the [Therapeutic Goods \(Permissible Ingredients\) Determination in June 2018](#). This included clarification of the Poisons Standard requirements for arbutin. As of 1 July 2018 ingredients known to contain arbutin will have arbutin listed as a mandatory component with associated specific requirements in line with the Poisons Standard. The affected ingredients include *Achillea millefolium*, *Arctostaphylos uva-ursi* (leaf), *Chimaphila umbellata*, *Kalmia latifolia*, *Ledum palustre*, *Origanum majorana*, *Pyrus communis*, *Pyrus pyrifolia*, *Rhododendron ferrugineum*, *Turnera diffusa*, *Vaccinium vitis-idaea* (leaf). The concentration of arbutin in the medicine must be no more than 25 mg/kg or 25mg /L or 0.0025 per cent unless used on the hair. This cut-off is based on the exemption in Part 1, Interpretation of the Poisons Standard, which states a scheduled substance (in Schedules 1 to 6 only) can be present at a concentration below 10 mg per litre or 10 mg per kg. The 25 mg/kg or 25mg /L or 0.0025 per cent cut-off for arbutin has been calculated based on the amount of hydroquinone converted into arbutin.

Hair preparations

In July 1987, the DPSC agreed to a general exemption from scheduling for ≤ 1 per cent hydroquinone in hair preparations.

In October 2008, the NDPSC noted that the European Union (EU) cut-offs for hydroquinone as an unapproved cosmetic ingredient (≤ 0.3 per cent in hair dyes) were more restrictive than the Poisons Standard controls (allowing ≤ 1 per cent).

In February 2009, the NDPSC considered a proposal to amend the exemption for use in hair dyes from 1 per cent to 0.3 per cent, in line with the European Union (EU) cut-offs. The NDPSC decided to amend the exemption for hair preparations containing hydroquinone from 1 per cent to 0.3 per cent or less.

Salts and derivatives

In May 1987, the DPSC noted that monobenzone was actually more potent than hydroquinone and agreed to foreshadow that it should be in Schedule 4, together with other derivatives of hydroquinone for human therapeutic or cosmetic use, with no exceptions (whereas hydroquinone had a Schedule 2 entry). The NDPSC also noted that the other ether derivatives of hydroquinone were more potent than hydroquinone and had a similar side effect level to monobenzone.

In July 1987, the DPSC amended the foreshadowed monobenzone entry by specifying capture of 'other alkyl ethers of hydroquinone for human therapeutic use or cosmetic use' rather than all derivatives. [No reason was recorded]. This remains the wording in the current monobenzone entry.

In February and June 2009, the NDPSC considered the scheduling of hydroquinone for therapeutic and cosmetic use. Both meetings supported deferring a decision on the scheduling of hydroquinone in skin bleaching products (for external therapeutic use) until the USFDA report was available. The Committee agreed that arbutin for cosmetic use should continue to be scheduled as a derivative of hydroquinone and that a cross reference with glycosylated hydroquinone in the Poisons Standard index be created.

Australian regulations

- According to the [TGA Ingredient Database](#):
 - Arbutin is not available for use as an active ingredient or excipient in any application. However, arbutin is available for use as an equivalent ingredient in export only and listed medicines.
 - Hydroquinone derivatives calculated as anhydrous arbutin are not available for use as an active ingredient or excipient in any application. However, it is available for use as equivalent ingredients in export only and over the counter medicines.
 - The following plant extracts are sources of arbutin and are available for use as follows:
 - *Achillea millefolium*: available for use as an active ingredient in export only, listed medicines, over the counter, and prescription medicines. Available for use as a homoeopathic ingredient in listed medicines. Available for use as an excipient ingredient in export only, listed medicines, over the counter, and prescription medicines. Not available as an equivalent ingredient in any application.
 - *Arctostaphylos uva-ursi*: available for use as an active ingredient in export only, listed medicines, over the counter and prescription medicines. Available for use as a homoeopathic ingredient in listed medicines. Available for use as an excipient ingredient in export only, listed medicines, over the counter and prescription medicines. Not available as an equivalent ingredient in any application.
 - *Kalmia latifolia*: available for use as an active ingredient in export only, listed medicines, over the counter and prescription medicines. Available for use as a homoeopathic ingredient in listed medicines. Available for use as an excipient ingredient in prescription medicines. Not available as an equivalent ingredient in any application.
 - *Ledum palustre*: available for use as an active ingredient in export only, listed medicines, over the counter and prescription medicines. Available for use as a homoeopathic ingredient in listed medicines. Available for use as an excipient ingredient in prescription medicines. Not available as an equivalent ingredient in any application.
 - *Origanum majorana*: available for use as an active ingredient in export only, listed medicines, over the counter, and prescription medicines. Available for use as a homoeopathic ingredient in listed medicines. Available for use as an excipient ingredient in prescription medicines. Not available as an equivalent ingredient in any application.
 - *Pyrus communis*: available for use as an active ingredient in export only, listed medicines, over the counter and prescription medicines. Available for use as a homoeopathic ingredient in listed medicines. Available for use as an excipient ingredient in devices,

export only, listed medicines, over the counter and prescription medicines. Not available as an equivalent ingredient in any application.

- *Pyrus pyrifolia*: available for use as an active ingredient in listed medicines and prescription medicines. Available for use as a homoeopathic ingredient in listed medicines. Available for use as an excipient ingredient in prescription medicines. Not available as an equivalent ingredient in any application.
- *Rhododendron ferrugineum*: available for use as an active ingredient in export only, listed medicines, over the counter and prescription medicines. Available for use as a homoeopathic ingredient in listed medicines. Available for use as an excipient ingredient in prescription medicines. Not available as an equivalent ingredient in any application.
- *Turnera diffusa*: available for use as an active ingredient in export only, listed medicines, over the counter and prescription medicines. Available for use as a homoeopathic ingredient in listed medicines. Available for use as an excipient ingredient in export only, listed medicines, over the counter and prescription medicines. Not available as an equivalent ingredient in any application.
- *Vaccinium vitis-idaea*: available for use as an active ingredient in listed medicines and prescription medicines. Available for use as a homoeopathic ingredient in listed medicines. Available for use as an excipient ingredient in prescription medicines. Not available as an equivalent ingredient in any application.

- As of 8 May 2019, there are no medicines currently active on the [Australian Register of Therapeutic Goods \(ARTG\)](#)⁴³ that contain arbutin as an active ingredient. However, the following plants, which are known sources of arbutin, are found on the ARTG as follows:

- *Achillea millefolium*: 17 products;
- *Arctostaphylos uva-ursi*: 21 products;
- *Kalmia latifolia*: 2 products;
- *Ledum palustre*: 3 products;
- *Origanum majorana*: 12 products;
- *Pyrus communis*: 4 products;
- *Turnera diffusa*: 51 products; and
- *Vaccinium vitis-idaea*: 1 product.

- The following plant extracts which are sources of arbutin are permitted to be included in listed medicines according to the [Therapeutic Goods \(Permissible Ingredients\) Determination No.2 of 2019](#)⁴⁴ as follows:

Item	Ingredient name	Purpose	Specific requirements
333	<i>Achillea millefolium</i>	A, E, H	<p>Arbutin is a mandatory component of <i>Achillea millefolium</i>.</p> <p>The concentration of arbutin in the medicine must be no more than 25 mg/kg or 25mg/L or 0.0025% unless used on the hair.</p> <p>When for use on hair, the concentration of arbutin in the medicine must be no more than 0.74%.</p>

⁴³ <https://www.tga.gov.au/artg>

⁴⁴ <https://www.legislation.gov.au/Series/F2019L00620>

646	<i>Arctostaphylos uva-ursi</i>	A, E, H	<p>Arbutin is a mandatory component of <i>Arctostaphylos uva-ursi</i>.</p> <p>The concentration of arbutin in the medicine must be no more than 25 mg/kg or 25mg/L or 0.0025% unless used on the hair.</p> <p>When for use on hair, the concentration of arbutin in the medicine must be no more than 0.74%.</p>
1314	<i>Chimaphila umbellata</i>	A, H	<p>Arbutin is a mandatory component of <i>Chimaphila umbellata</i>.</p> <p>The concentration of arbutin in the medicine must be no more than 25 mg/kg or 25mg/L or 0.0025% unless used on the hair.</p> <p>When for use on hair, the concentration of arbutin in the medicine must be no more than 0.74%.</p>
2826	<i>Kalmia latifolia</i>	A, H	<p>Arbutin is a mandatory component of <i>Kalmia latifolia</i>.</p> <p>The concentration of arbutin in the medicine must be no more than 25 mg/kg or 25mg /L or 0.0025% unless used on the hair.</p> <p>When for use on hair, the concentration of arbutin in the medicine must be no more than 0.74%.</p>
2946	<i>Ledum palustre</i>	A, H	<p>Arbutin is a mandatory component of <i>Ledum palustre</i>.</p> <p>The concentration of arbutin in the medicine must be no more than 25 mg/kg or 25mg/L or 0.0025% unless used on the hair.</p> <p>When for use on hair, the concentration of arbutin in the medicine must be no more than 0.74%.</p> <p>When the route of administration is other than topical, the maximum recommended daily dose must not contain more than 0.001 mg of the equivalent dry herbal material of <i>Ledum palustre</i>.</p>
3575	<i>Origanum majorana</i>	A, H	<p>Arbutin is a mandatory component of <i>Origanum majorana</i>.</p> <p>The concentration of arbutin in the medicine must be no more than 25 mg/kg or 25mg/L or 0.0025% unless used on the hair.</p> <p>When for use on hair, the concentration of arbutin in the medicine must be no more than 0.74%.</p> <p>When the plant preparation is oil or distillate, the nominal capacity of the container must be no more than 50 millilitres.</p> <p>When the concentration of <i>Origanum majorana</i> oil or distillate in the preparation is greater than 50%, a restricted flow insert must be fitted on the container and following warning statement is required on the medicine label:</p> <p>- (CHILD) 'Keep out of reach of children' (or words to that effect).</p>

4204	<i>Pyrus communis</i>	A, E, H	<p>Arbutin is a mandatory component of <i>Pyrus communis</i>.</p> <p>The concentration of arbutin in the medicine must be no more than 25 mg/kg or 25mg/L or 0.0025% unless used on the hair.</p> <p>When for use on hair, the concentration of arbutin in the medicine must be no more than 0.74%.</p>
4205	<i>Pyrus pyrifolia</i>	A, H	<p>Arbutin is a mandatory component of <i>Pyrus pyrifolia</i>.</p> <p>The concentration of arbutin in the medicine must be no more than 25 mg/kg or 25mg/L or 0.0025% unless used on the hair.</p> <p>When for use on hair, the concentration of arbutin in the medicine must be no more than 0.74%.</p>
4284	<i>Rhododendron ferrugineum</i>	A, H	<p>Arbutin is a mandatory component of <i>Rhododendron ferrugineum</i>.</p> <p>The concentration of arbutin in the medicine must be no more than 25 mg/kg or 25mg/L or 0.0025% unless used on the hair.</p> <p>When for use on hair, the concentration of arbutin in the medicine must be no more than 0.74%.</p>
5022	<i>Turnera diffusa</i>	A, E, H	<p>Arbutin is a mandatory component of <i>Turnera diffusa</i>.</p> <p>The concentration of arbutin in the medicine must be no more than 25 mg/kg or 25mg/L or 0.0025% unless used on the hair.</p> <p>When for use on hair, the concentration of arbutin in the medicine must be no more than 0.74%.</p>
5070	<i>Vaccinium vitis-idaea</i>	A, H	<p>Arbutin is a mandatory component of <i>Vaccinium vitis-idaea</i>.</p> <p>The concentration of arbutin in the medicine must be no more than 25 mg/kg or 25mg/L or 0.0025% unless used on the hair.</p> <p>When for use on hair, the concentration of arbutin in the medicine must be no more than 0.74%.</p>
A = active ingredient, E = excipient, H = homoeopathic preparation ingredient			

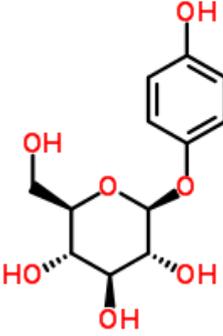
International regulations

- The [European Chemicals Agency \(ECHA\)](#) hazard classification for arbutin is, 'Warning! According to the classification provided by companies to ECHA in CLP notifications this substance causes serious eye irritation, causes skin irritation and may cause respiratory irritation'.
- In 2018, the [European Medicines Agency \(EMA\) Herbal Medicinal Products Committee \(HMPC\)](#) concluded that on the basis of its long-standing use, bearberry leaf preparations (*Arctostaphylos uva-ursi*) can be used for treating symptoms of mild, recurrent infections in the lower urinary tract, such as a burning sensation when passing urine and/or frequently passing urine. The HMPC conclusions on the use of these bearberry leaf medicines for lower urinary tract infections are based on their 'traditional use'. This means that, although there is insufficient evidence from clinical trials, the effectiveness of these herbal medicines is plausible and there is evidence that they have been used safely in this way for at least 30 years (including at least 15 years within the EU). Moreover, the intended use does not require medical supervision. In its assessment, the HMPC considered laboratory studies which showed bearberry leaf preparations to have antibacterial action. No clinical studies are available with preparations containing only bearberry leaf.

- European Scientific Cooperative on Phytotherapy (ESCOPE) supports the use of *Arctostaphylos uva-ursi* for uncomplicated infections of the lower urinary tract, such as cystitis. The ESCOP monograph states that *Arctostaphylos uva-ursi* should contain a minimum of 7.0% anhydrous arbutin.
- In the United States (US), the use of bearberry (extract of *uva ursi*) and bearberry fluidextract (extract of bearberry) as a 'menstrual/diuretic' is regulated under 21 CFR 310.545(a)(24); marketing of products for these uses requires an approved new drug application.

Substance summary

Table 1: Chemical information for arbutin

Property	Arbutin
Chemical structure	
Molecular formula	C ₁₂ H ₁₆ O ₇
Molecular weight	272.25 g/mol
CAS name	β-D-Glucopyranoside, 4-hydroxyphenyl
CAS number	497-76-7
IUPAC and/or common and/or other names	Arbutin, arbutoside, (2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i> ,6 <i>S</i>)-2-Hydroxymethyl-6- (4-hydroxyphenoxy)oxane-3,4,5-triol (IUPAC), Hydroquinone 1- <i>O</i> -beta- <i>D</i> -glucopyranoside, Hydroquinone β- <i>D</i> -glucopyranoside, 4-hydroxyphenyl-beta- <i>D</i> -glucopyranoside

Hydroquinone 1-*O*-beta-*D*-glucopyranoside is the chemical identity of arbutin (Quintus 2005). The molecular weight is 272.25 g/mol (de Arriba 2013).

The three major metabolites of arbutin *in vivo* in order of decreasing concentration are hydroquinone glucuronide > hydroquinone sulfate > free hydroquinone (Schindler 2002).

Arbutin is a naturally occurring phenolic glycoside in many widely consumed food plants, including blueberry, cranberry (and other *Vaccinium* species), pear, bean, wheat, coffee, wine and broccoli (Deisinger 1996, Blaut 2006, Booth 2012). The amount of arbutin in a pear (12.7 mg) would be metabolised to hydroquinone in 1-4 hrs (Blaut 2006). A typical dietary consumption of arbutin rich foods of 2-3 cups of tea/coffee, plus 1 glass of red wine in a person of 60 kg would result in exposure of free hydroquinone from 0.66-4.5 mcg/kg bw/d to 9.3 mcg/kg bw/d (de Arriba 2013).

Summary of pre-meeting public submissions

Nine (9) submissions were received in response to [the notice published under regulation 42ZCZK advising of the proposed amendment](#). Seven (7) were in support and two (2) opposed the proposed amendments (one (1) of which suggested further amendments).

The main points in support of the proposed amendments:

- Arbutin is a constituent of a number of herbs, however the scheduling has particularly affected the supply of herbal preparations of bearberry (*Arctostaphylos uva ursi*) and Damiana (*Turnera*

diffusa). These herbal preparations that contain arbutin have a long history of use by western herbal medicine practitioners in Australia without adverse effects. The un-scheduling of naturally occurring arbutin in herbal medicines does not present an unacceptable risk to human health.

- Naturally occurring arbutin in herbal preparations for internal human therapeutic use should not require restriction via scheduling as they have not been shown to present an unacceptable risk to public health. Arbutin itself is now approved for use in cosmetic products in the EU, with listed functions including antioxidant, skin conditioning and skin lightening.
- The NDPS record of reason from 2009 stated ‘...that until more robust data was available regarding the actual risk of arbutin, then it remained appropriate to take a conservative approach and control arbutin under the current scheduling of hydroquinone as a derivative...’. Since the 2009 consideration, new data on the safety of arbutin when used in cosmetics has become available. The European Commission’s Scientific Committee on Consumer Safety (SCCS) published two opinions relating to the substances α -arbutin and β -arbutin which came to the following conclusions:
 - The SCCS considers the use of α -arbutin safe for consumers in cosmetic products in a concentration up to 2% in face creams and up to 0.5 % in body lotions.
 - The SCCS considers the use of β -arbutin to be safe for consumers in cosmetic products in a concentration up to 7% in face creams provided that the contamination of hydroquinone in the cosmetic formulations remain below 1 ppm.⁴⁵ Therefore, the cosmetic use of arbutin can now be reconsidered to allow its use in line with the findings of the SCCS opinions as detailed above.
- Pharmacists have noted that some arbutin-containing products carry claims that alpha-arbutin is ‘much stronger in effect than arbutin or beta-arbutin’. As per the SCCS opinion on alpha and beta arbutin, the ACMS should consider whether different concentration limits need to be applied to the two arbutin derivatives if they are to be included in the Poisons Standard.
- The proposed limit for oral herbal preparations of 500 mg or less of arbutin per recommended daily dose appears to be within acceptable range. However, it is also reported that traditional use of arbutin can only be recommended for females. The use of arbutin by men is only recommended when advised by a medical practitioner due to the risk of more severe infections (and not on the basis of traditional use). There is also reference to the recommended time of use being limited to two weeks.
- Specific consideration is also warranted on whether different or additional controls should be applied for:
 - Different arbutin derivatives for external use;
 - The use of oral arbutin preparations for urinary tract infections in males; and
 - The recommended duration of use of oral arbutin preparations.
- The individual listing of arbutin rather than the current arrangement of being captured as a derivative of hydroquinone, with a cross-reference to arbutin in the index will ensure that the requirements for products containing arbutin are clear and more easily identified.
- The proposed upper limit of 500 mg of arbutin or less per daily recommended dosage is well within the EMA safe level of 840 mg per day as stated in their assessment report on *Arctostaphylos uva-ursi*.
- Whilst arbutin can be hydrolysed to hydroquinone, pharmacokinetic data indicate that it is stable in gastric acid and only deglycosylated once in the liver, whereby the liberated hydroquinone is immediately conjugated to hydroquinone glucuronide and hydroquinone sulfate. Subsequent hydrolysis to hydroquinone only occurs at the point of excretion in the urine, providing the known urinary antimicrobial effect of herbal medicines such as *Arctostaphylos uva-ursi*.

⁴⁵ https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_169.pdf

- The molar mass of arbutin is 272.243 g/mol compared to 110.112 g/mol for hydroquinone. Thus, from a toxicological perspective, arbutin and hydroquinone cannot be regarded as equivalent when consumed orally in the context of a herbal preparation

The main points in opposition of the proposed amendments:

- The proposed Schedule 2 entry is unnecessarily restrictive in relation to human external therapeutic and cosmetic use products. In 2015, the SCCS published that they consider β -arbutin to be safe for consumers in cosmetic products in a concentration up to 7% in face creams provided the contamination of hydroquinone remains below 1 ppm. In 2015, the SCCS also published their opinion that α -arbutin is safe for consumers in cosmetic products in a concentration in face creams and up to 0.5% in body lotions.
- Given the above, the following alternative wording was proposed in the public submission:

Schedule 4 – New Entry

ARBUTIN in preparations for human therapeutic or cosmetic use except:

- a) when included in Schedule 2; or
- b) in hair preparations containing 0.75 per cent; or
- c) in cosmetic nail preparations containing 0.05 per cent; or
- d) in oral herbal preparations containing 500 mg or less of arbutin per recommended daily dose; or
- e) in preparations for human external therapeutic or cosmetic use for the face containing not more than 2 per cent; or
- f) in preparations for human external therapeutic or cosmetic use for the body containing not more than 0.05 per cent.

Schedule 2 – New Entry

ARBUTIN in preparations for human external therapeutic or cosmetic use (excluding hair preparations and cosmetic nail preparations) containing between more than 2 percent and not more than 5 percent of arbutin except:

- a) in hair preparations containing 0.75 percent; or
- b) in cosmetic nail preparations containing 0.05 percent; or
- c) in preparations for human external therapeutic or cosmetic use for the face containing not more than 2 percent; or
- d) in preparations for human external therapeutic or cosmetic use for the body containing not more than 0.05 percent.

- As evidenced by the SCCS reports, topical arbutin at the proposed limits does not pose a risk of harm to public health.
- Benefits of the proposed limit include permitting greater access by consumers. The ability of consumers to manage minor skin imperfections without posing a burden on the public purse through unnecessary medical consultations as well as relieve undue pressure on pharmacists so that they may concentrate on more appropriate health concerns.
- The wording under this proposal is for topical application in human therapeutic or cosmetic goods. The LD₅₀ value via the dermal route showed to be greater than 928 mg/kg bw (the technically applicable maximal dose). The tested animals showed no signs of harm for application via dermal route. It is expected this would likely be similar for humans.
- One of the main issues with arbutin is the presence of hydroquinone, and there is no mention of any residue limits on hydroquinone. This should be added for clarity.

Summary of Joint ACCS-ACMS advice/recommendations to the Delegate

The Committee recommended that a new Schedule 4 entry be created for arbutin in the Poisons Standard as follows:

Schedule 4 – New Entry

ARBUTIN **except** in oral herbal preparations containing 500 mg or less of arbutin per recommended daily dose.

INDEX – Amend Entry

ARBUTIN

cross reference: ~~HYDROQUINONE~~

Schedule 4

The Committee also recommended an amendment to the hydroquinone index entry as follows:

Index – Amend Entry

HYDROQUINONE

cross reference: ~~ARBUTIN~~, GLYCOSYLATED HYDROQUINONE, MONOBENZONE

Schedule 6

Schedule 4

Schedule 2

The Committee recommended an implementation date of 1 June 2020.

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; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice included:

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

- Benefits:
 - Benefits relate mainly to traditional use. It is in many listed herbal medicines and herbal ingredients available for use to practitioners.
- Risks:
 - Little risk as <0.6% excreted as free hydroquinone in urine.
 - In common foods and herbs with little toxic effects.
 - The risks of arbutin are associated with potential for hydrolysis to form free hydroquinone, which is regarded as having higher level of risk compared to arbutin.

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

- Arbutin is commonly found in foods and is a component of 11 herbal ingredients included in the TGA Permitted Ingredients Determination, which are available to sponsors to be included in products listed on the ARTG. There are many listed medicines containing these ingredients that have arbutin as a mandatory component.
- *Arctostaphylos uva-ursi*, a major source of arbutin, has a history of traditional use in symptoms of cystitis. The TGA restricts indications for listed medicines to those in the Permitted Indications list. The other 10 herbal ingredients have a traditional use in a variety of other indications.

(c) *the toxicity of a substance:*

- Consistent with Schedule 4.
- Toxicity concerns relate mainly to risks associated with conversion to hydroquinone.

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

- Nil.

(e) *the potential for abuse of a substance:*

- No evidence of abuse or misuse of the affected herbal medicines.

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

- Use in men: For *Arctostaphylos uva-ursi*, community EMA monograph (2018) notes that clinical use in men is not recommended based on risk of complicated UTI in men above age 50 which may be due to benign prostatic hyperplasia and thus require the assessment by a medical practitioner. This may be helped by labelling.

Delegate's considerations

In making this interim decision, I have considered the following material:

- The application to amend the current Poisons Standard with respect to arbutin;
- Joint Meeting of the Advisory Committee on Chemicals Scheduling and the Advisory Committee on Medicines Scheduling's advice;
- The public submissions received before the [first closing date](#);
- Section 52E of the *Therapeutic Goods Act 1989*, in particular: (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; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health;
- The Australian Health Ministers' Advisory Council's [Scheduling Policy Framework](#) (SPF 2018); and
- The Australian Health Ministers' Advisory Council's [Scheduling Handbook](#) (V 1.0, January 2018).

Reasons for interim decision

I agree with the Committee's finding that the relevant matters of section 52E of the *Therapeutic Goods Act 1989* are: (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; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

In my view, the relevant parts of the Scheduling Policy Framework (SPF) 2018 are the Scheduling Factors for Schedule 4.

I have made the decision to amend the current Poisons Standard to create a new Schedule 4 entry for arbutin and I have set out my reasons below.

I am of the view that arbutin and hydroquinone are separate substances of differing toxicity and molecular make up and as a result, should each have separate entries in the Poisons Standard. I agree with the data presented in the application that arbutin has a significant history of traditional use and is present in many food sources, as well as being a component of eleven herbal ingredients included in the TGA Permitted Ingredients Determination.

I have taken into consideration the toxicological data presented and I find that the proposed cut-off of 500 mg or less of arbutin per recommended daily dose as proposed by the Applicant to be acceptable. The amount of free hydroquinone following absorption of a 500 mg dose of arbutin would result in acceptable amounts of free hydroquinone in accordance with the cut-offs for hydroquinone in the Poisons Standard. I acknowledge that this cut off is well within the safe levels outlined by the

European Scientific Cooperative on Phytotherapy (ESCOP), the European Medicines Agency (EMA) monograph and the British Pharmacopoeia (PB) monograph.

I find the Schedule 4 entry for arbutin appropriate, noting that any dosage of arbutin above the cut-off requires medical management by a general practitioner.

I have considered that the scheduling proposal provided limitations on the use of arbutin in cosmetic products and that these limits were a direct conversion of the hydroquinone cut-offs as set out in the Poisons Standard. Several public submissions suggested adopting the cut-offs outlined in the European (Scientific Committee on Consumer Safety) report. However, as the nature of the current scheduling application and associated toxicological data was in reference to the traditional use of arbutin in herbal preparations, I find that on balance, the topical use of arbutin should be considered in a separate consultation. This would allow for specific consideration of toxicity data on the dermal effects of arbutin.

I note that the current decision will affect the Permissible Ingredients Determination, which will require updating to the eleven herbs cross referenced in the list.