Australian Government
Department of Health
Therapeutic Goods Administration

Final decisions and reasons for decisions by delegates of the Secretary to the Department of Health

23 March 2017

(ACCS, ACMS and Joint ACCS-ACMS meetings – November 2016)

Notice under subsections 42ZCZS/42ZCZX of the Therapeutic Goods Regulations 1990 (the Regulations)

The delegates of the Secretary to the Department of Health hereby give notice of delegates' final decisions for amending the *Poisons Standard* (commonly referred to as the *Standard for the Uniform Scheduling of Medicines and Poisons* - SUSMP) under subsections 42ZCZS/42ZCZX of the Therapeutic Goods Regulations 1990 (the Regulations). This notice also provides the reasons for each decision and the date of effect (implementation date) of the decision.

The delegates' final decisions and reasons relate to:

- scheduling proposals referred to the November 2016 meeting of the Advisory Committee on Chemicals Scheduling (ACCS#18);
- scheduling proposals referred to the November 2016 meeting of the Advisory Committee on Medicines Scheduling (ACMS#19);
- scheduling proposals referred to the November 2016 meeting of the Joint Advisory Committee on Chemicals and Medicines Scheduling (Joint ACCS-ACMS#14)
- scheduling proposals considered as delegate-only matters, i.e. not referred to an expert advisory committee.

Scheduling proposals referred to the expert advisory committees

Pre-meeting public notice

On 4 August 2016 and 22 September 2016, under subsection 42ZCZK of the *Therapeutic Goods Regulations 1990* (the Regulations), the delegate published a pre-meeting public notice on the TGA website which specified the proposed amendments to the current Poisons Standard and invited public comment.

The pre-meeting consultation periods were each open for public comment for 20 business days and closed on 1 September 2016 and 20 October 2016.

In accordance with subsection 42ZCZL of the Regulations redacted versions of public submissions received in response this invitation were published on 2 February 2017 on the TGA website at https://www.tga.gov.au/public-submissions-scheduling-matters.

Interim decisions

November 2016 ACCS#18, ACMS#19 and Joint ACCS-ACMS#14

On 2 February 2017, in accordance with subsection 42ZCZN of the Regulations, the delegate made an interim decision on an application and under subsection 42ZCZP of the Regulations, the interim decision and the reasons for the decision was published on TGA website. Further submissions were also invited from the applicants and parties who made valid pre-meeting submissions. The inivitation to make submissions was open for 10 business days and closed on 16 February 2017.

Redacted versions of public submissions will be published at Public submissions on scheduling matters on or after the date of this notice.

Final decisions

In accordance with subsection 42ZCZR of the Regulations, if a delegate makes an interim decision on an application, the delegate may make a final decision either, confirming, varying or setting aside the interim decision, but only after considering any valid submissions received in response to the interim decisions.

Matters not referred to an advisory committee

According to subsections 42ZCZT/42ZCZU of the Regulations a delegate may decide not to refer a scheduling proposal to an expert advisory committee for advice and instead may make a delegate-only decision. When deciding not to refer a matter to a committee, the delegate considers the scheduling guidelines as set out in the *Scheduling Policy Framework for Chemicals and Medicines* (SPF, 2015), available at SPF, February 2015.

Publishing of the amendments to the Poisons Standard

The amendments to the Schedules, Appendices or other parts of the *Poisons Standard* are published electronically on the Federal Register of Legislation (FRL) as amendments to the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) prior to the date of effect (implementation date) of the final decisions. Further information, including links to the *Poisons Standard* on FRL, is available at SUSMP.

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Part A - Final decisions on matters referred to an expert advisory committee

1. Advisory Committee on Chemicals Scheduling (ACCS#18)

Summary of delegate's final decisions

The following final decisions have an implementation date of 1 February 2018 unless otherwise specified.

Substance	Final decision
Pegbovigrastim	**Appendix B – New Entry** PEGBOVIGRASTIM **Part 1 – Reasons for entry** a (low toxicity) **Part 2 – Area of use** 2.1 (For animal use) **Implementation date:** 1 June 2017.

Substance	Final decision
3-nitro-*p*-hydroxyethylaminophenol Also known as: 4-[(2-Hydroxyethyl)amino]-3-nitrophenol	**Schedule 6 - New Entry** 3-NITRO-*p*-HYDROXYETHYLAMINOPHENOL **except**: a) in non-oxidative hair dye preparations containing 1.85 per cent or less of 3-nitro-*p*-hydroxyethylaminophenol after mixing when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and Written in letters not less than 1.5 mm in height; or b) in oxidative hair dye preparations containing 3 per cent or less of 3-nitro-*p*-hydroxyethylaminophenol after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and Written in letters not less than 1.5 mm in height. **Appendix E, Part 2 – New Entry** 3-NITRO-*p*-HYDROXYETHYLAMINOPHENOL Standard statement: E1 (if in eyes wash out immediately with water). **Appendix F, Part 3 – New Entry** 3-NITRO-*p*-HYDROXYETHYLAMINOPHENOL Warning statements: 28 ((over) (repeated) exposure may cause sensitisation). **Index - New Entry** **3-NITRO-*p*-HYDROXYETHYLAMINOPHENOL** cross reference: 4-[(2-hydroxyethyl)amino]-3-nitrophenol Schedule 6 Appendix E, Part 2 Appendix F, Part 3

Substance	Final decision
Hydroxyethyl-3,4-methylenedioxyaniline	**Schedule 6 – New Entry** HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE (including its salts) **except** in oxidative hair dye preparations containing 1.5 per cent or less of hydroxyethyl-3,4-methylenedioxyaniline after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and Written in letters not less than 1.5 mm in height. **Appendix E, Part 2 – New Entry** HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE Standard statements: E1 (if in eyes wash out immediately with water), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water). **Appendix F, Part 3 – New Entry** HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

Substance	Final decision
1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride	**Schedule 6 – New entry** 1,3-BIS(2,4-DIAMINOPHENOXY)PROPANE (including its salts) **except** when in hair dye preparations containing 1.2 per cent or less of 1,3-bis(2,4-diaminophenoxy)propane after mixing when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and Written in letters not less than 1.5 mm in height. **Appendix E, Part 2 – New Entry** 1,3-BIS(2,4-DIAMINOPHENOXY)PROPANE Standard statements: E1 (if in eyes wash out immediately with water), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water). **Appendix F, Part 3 – New Entry** 1,3-BIS(2,4-DIAMINOPHENOXY)PROPANE Warning statements: 28 ((over) (repeated) exposure may cause sensitisation), 79 (Will irritate eyes). Safety directions: 1 (Avoid contact with eyes). **Index – New entry** **1,3-BIS(2,4-DIAMINOPHENOXY)PROPANE** Schedule 6 Appendix E, Part 2 Appendix F, Part 3
2,2'-[(4-Amino-3-nitrophenyl)imino]bisethanol and its monohydrochloride	**Schedule 6 – New Entry** 2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL (including its salts) **except**: a) in non-oxidative hair dye preparations containing 2.5 per cent or less of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol after mixing when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying

Substance	Final decision
	directions should be made before use, and Written in letters not less than 1.5 mm in height; or b) in oxidative hair dye preparations containing 1.25 per cent or less of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and Written in letters not less than 1.5 mm in height. **Appendix E, Part 2 – New Entry** 2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL Standard statements: E1 (if in eyes wash out immediately with water). **Appendix F, Part 3 – New Entry** 2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL Warning statements: 28 ((over) (repeated) exposure may cause sensitisation). **Index – New Entry** **2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL** cross reference: HC RED 13 Schedule 6 Appendix E, Part 2 Appendix F, Part 3 **HC RED 13** cross reference: 2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL

Substance	Final decision
2-[(4-Amino-2-methyl-5-nitrophenyl)amino]-ethanol Also known as: HC Violet 1	**Schedule 6 – New Entry** HC VIOLET 1 (2-[(4-amino-2-methyl-5-nitrophenyl)amino]-ethanol **except**: a) in non-oxidative hair dye preparations containing 0.28 per cent or less of HC Violet 1 after mixing when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and Written in letters not less than 1.5 mm in height; or b) in oxidative hair dye preparations containing 0.25 per cent or less of HC Violet 1 after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements: KEEP OUT OF REACH OF CHILDREN, and WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and Written in letters not less than 1.5 mm in height. **Appendix E, Part 2 – New Entry** HC VIOLET 1 Standard statements: E1 (if in eyes wash out immediately with water). **Appendix F, Part 3 – New Entry** HC VIOLET 1 Warning statements: 28 ((over) (repeated) exposure may cause sensitisation). **Index – New Entry** **HC VIOLET 1** cross reference: 2-[(4-AMINO-2-METHYL-5-NITROPHENYL)AMINO]-ETHANOL Schedule 6 Appendix E, Part 2 Appendix F, Part 3

Substance	Final decision
Abamectin	**Schedule 5 – Amend Entry** ABAMECTIN: a) in preparations, for internal use for the treatment of animals, containing 1 per cent or less of abamectin; or b) in gel formulations containing 0.05 per cent or less of abamectin in applicators containing 50 mg or less of abamectin. **Implementation date:** 1 June 2017.
1-Deoxy-1-(methylamino)-D-glucitol-*N*-coco acyl derivatives	**Schedule 6 – New Entry** 1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL *N*-COCO ACYL DERIVATIVES **except:** a) in cosmetic rinse-off preparations containing 8 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives when labelled with the following statement: IF IN EYES WASH OUT IMMEDIATELY WITH WATER, or b) in household cleaning preparations, other than those intended to be sprayed, containing 10 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives when labelled with the following statement: IF IN EYES WASH OUT IMMEDIATELY WITH WATER. **Appendix E, Part 2 – New Entry** 1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL *N*-COCO ACYL DERIVATIVES Standard statement: E1 (if in eyes wash out immediately with water). **Appendix F, Part 3 – New Entry** 1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL *N*-COCO ACYL DERIVATIVES Warning statement: 79 (Will irritate eyes). Safety direction: 1 (Avoid contact with eyes) **Index – New Entry** **1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL *N*-COCO ACYL DERIVATIVES** cross reference: cocoyl methyl glucamaide Schedule 6 Appendix E, Part 2 Appendix F, Part 3

Substance	Final decision
o-Toluidine and *o*-Anisidine	**Schedule 10 – New Entries** *o*-TOLUIDINE (excluding derivatives) in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows **except** in preparations containing 0.001 per cent or less of *o*-toluidine. *o*-ANISIDINE (excluding derivatives) in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows **except** in preparations containing 0.001 per cent or less of *o*-anisidine.

1.1 Pegbovigrastim

Referred scheduling proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to consider whether pegbovigrastim requires scheduling.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Appendix B – New Entry

PEGBOVIGRASTIM.

The applicant's reasons for the request are:

- Pegbovigrastim is a modified form of the naturally-occurring bovine immunoregulatory cytokine, bG-CSF. The naturally-occurring protein is produced by mononuclear leukocytes, endothelial cells and fibroblasts. Pegbovigrastim is identical in primary sequence to the endogenously-produced protein with the exception of the addition of a terminal methionine and a single amino acid substitution whereby a novel amino acid, p-acetylphenylalanine, is incorporated into the protein to enable site-specific covalent attachment of a 20 kDa polyethylene glycol (PEG) polymer chain to the protein;
- No distribution, metabolism or excretion studies were submitted, however, these would be expected to be comparable to that of the endogenous protein. [Secretariat note: pegylation of CSFs, as well as other proteins, prolongs serum half-life (e.g. the pegylated form of human G-CSF has a half-life about 5 times longer than the non-pegylated form).] Distribution would be expected to be largely limited to the central compartment and the compound would be expected to be degraded to PEG and small peptides and amino acids which are excreted largely in urine;
- Pegbovigrastim was not a skin or eye irritant in rabbits. No skin sensitisation studies were submitted;
- No other toxicity studies were submitted for pegbovigrastim, but carcinogenicity and genotoxicity studies are generally not required for biological products. Pegbovigrastim might be expected to be of low toxicity as indicated by studies on the corresponding human colony stimulating factor;
- The safety profiles of the equivalent human product (PEG hG-CSF [pegfilgrastim, Neulasta®]), and the non-PEGylated product (filgrastim, Neupogen®), are well established in humans. These medicines are used for a number of purposes where patients are suffering neutropenia. The most common adverse reaction is bone pain. Severe adverse reactions to these products are rare, and have generally been observed upon repeated administration. Filgrastim showed low toxicity after both single and repeated doses in laboratory animal species; and

- The toxicity of polyethylene glycols is well understood and documented. Polyethylene glycols have low acute toxicity.

Current scheduling status and relevant scheduling history

Pegbovigrastim is not currently scheduled and has not been previously considered for scheduling; therefore a scheduling history is not available.

Three related substances (filgrastim, pegfilgrastim and lenograstim) have been considered for scheduling, and are currently in Schedule 4 for human therapeutic use.

International regulations

Products containing pegbovigrastim are registered in New Zealand, USA, Canada, the European Union (EU), Mexico and Brazil. Pegbovigrastim is subject to the following labelling requirements internationally:

- New Zealand – The following signal heading on labels are required, 'Restricted veterinary medicine', 'Keep out of reach of children' and 'For animal treatment only'.
- USA – Product Information leaflet include the following warning: 'Caution: federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.'

Substance summary

The pegylated bovine granulocyte colony stimulating factor (bG-CSF) (Figure 1) is almost identical to the endogenously produced bovine protein. The points of differences are:

- the addition of an amino terminal methionine
- a single amino acid substitution at position 133 whereby threonine in the endogenously produced bG-CSF is replaced with a novel amino acid, *p*-acetylphenylalanine glycol (F*) (Figure 1); this enables a site-specific covalent attachment of a 20 kDa polyethylene glycol (PEG) polymer chain to the protein through an oxime linkage
- pegylation of CSFs, as well as other proteins, prolongs serum half-life (e.g. the pegylated form of human G-CSF has a half-life about 5 times longer than the non-pegylated form

The proposed product will contain 15 mg pegbovigrastim/syringe for subcutaneous injection as an aid in the prevention of mastitis in dairy cows, through restoration of immune function in the periparturient period.

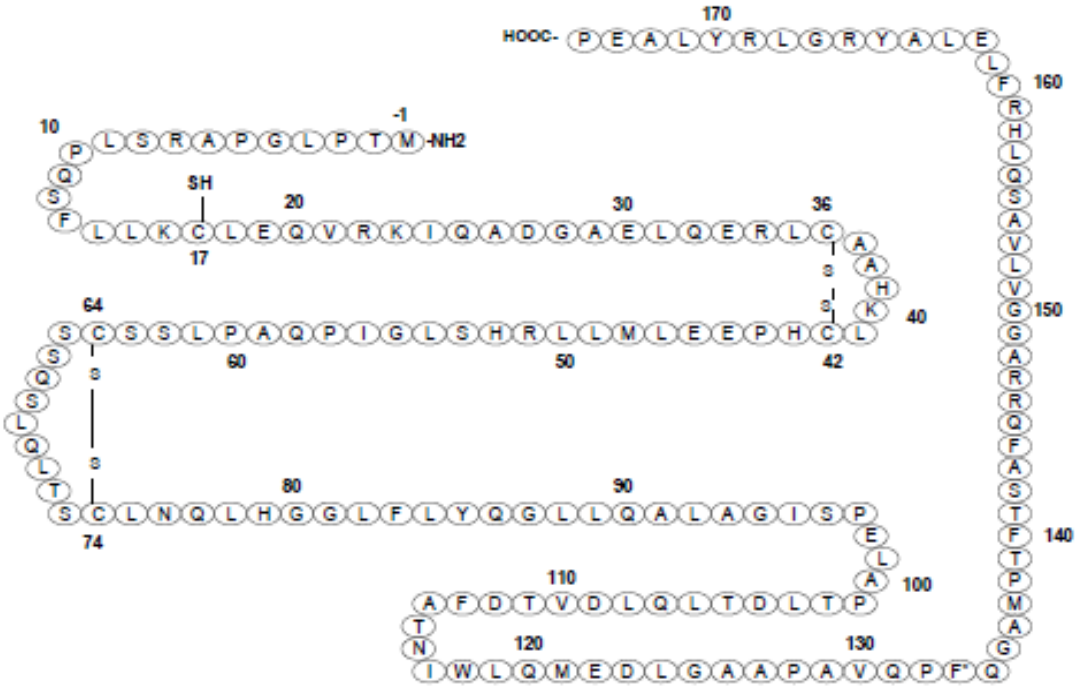


Figure 1.1: Amino acid sequence of pegbovigrastim.

Note the two di-sulfide bridges at positions 36 to 42 and 64 to 74. At position 133 (F*), threonine in the endogenously produced bG-CSF has been replaced with a novel amino acid, *p*-acetylphenylalanine glycol.

Table 1.1A: General information

Property	Pegbovigrastim
Amino acid sequence	MTPLGPARSLP QSFLLKCLEQ VRKIQADGAE LQERLCAAHK LCHPEELMLLRHSLGIPQAP LSSCSSQSLQ LTSCLNQLHG GLFLYQGLLQ ALAGISPELAPTLDTLQLDV TDFATNIWLQ MEDLGAAPAV QPFQGAMPTF TSAFQRRAGGVLVASQLHRF LELAYRGLRY LAEP
Molecular weight	40 600 Da
Empirical formula	$C_{859}H_{1370}N_{236}O_{248}S_9[C_2H_4O]n$ where n = 454
CAS number	1363409-60-2
IUPAC and/or common and/or other names	Pegylated bovine Granulocyte Colony Stimulating Factor (PEG bG-CSF)
SUSMP name	To be advised. 'Pegbovigrastim' or 'Pegylated bovine Granulocyte Colony Stimulating Factor' suggested.
Product name	Elanco Imrestor

The following information was extracted from the APVMA Human Health Risk Assessment Technical Report for pegbovigrastim (product name: Elanco Imrestor).

Table 1.1B: Acute toxicity end-points for pegbovigrastim

Toxicity	Species	Pegbovigrastim	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	No data	No data	No data
Acute dermal toxicity LD_{50} (mg/kg bw)	No data	No data	No data
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	No data	No data	No data
Skin irritation	Rabbit	Non-irritant	Non-irritant
Eye irritation	Rabbit	Non-irritant	Non-irritant
Skin sensitisation	No data	No data	No data

Pre-meeting public submissions

No pre-meeting submissions were received for pegbovigrastim.

Summary of ACCS advice to the delegate

The committee advised that a new Appendix B entry for pegbovigrastim be created in the Poisons Standard as follows:

Appendix B – New Entry

PEGBOVIGRASTIM

Part 1 – Reasons for entry
a (low toxicity)

Part 2 – Area of use
2.1 (For animal use)

The committee also advised an implementation date of **1 June 2017**.

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

The reasons for the advice comprised the following:

- Available and extrapolated evidence suggests pegbovigrastim is likely to have effects (though probably no serious effects) on humans if systemically absorbed/introduced.
- At present pegbovigrastim is likely to be registered only for use in periparturient cows.
- Pegbovigrastim has low toxicity.
- The presentation of pegbovigrastim is pre-filled single dose syringes that would be suitable for use by trained non-veterinarians.
- Pegbovigrastim is to be used under veterinary supervision.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)

Delegate's interim decision

The delegate's interim decision is to create a new Appendix B entry for pegbovigrastim for use in animals due to its low toxicity.

The proposed wording for the schedule entry is as follows:

Appendix B – New Entry

PEGBOVIGRASTIM

Part 1 – Reasons for entry
a (low toxicity)

Part 2 – Area of use
2.1 (For animal use)

The proposed implementation date is **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Low toxicity of pegbovigrastim
- At present pegbovigrastim is likely to be registered only for use in periparturient cows.
- The presentation of pegbovigrastim is pre-filled single dose syringes that would be suitable for use by trained non-veterinarians.
- Pegbovigrastim is to be used under veterinary supervision.
- Earliest possible implementation date.

Public submissions on the interim decision

No submissions were received for pegbovigrastim.

Delegate's final decision

The delegate has confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegate's final decision is to create a new Appendix B entry for pegbovigrastim for use in animals due to its low toxicity to be implemented on **1 June 2017**.

1.2 3-Nitro-*p*-hydroxyethylaminophenol (4-[(2-hydroxyethyl)amino]-3-nitrophenol)

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new Schedule 6 entry for 4-[(2-hydroxyethyl)amino]-3-nitrophenol in hair dye and eyelash/eyebrow colouring products and to determine whether an appropriate exemption cut-off is required.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 6 – New Entry

4-[(2-HYDROXYETHYL)AMINO]-3-NITROPHENOL **except** when used in hair dye colouring preparations containing 3 per cent or less of 4-[(2-hydroxyethyl)amino]-3-nitrophenol under oxidising conditions (after mixing with hydrogen peroxide), or containing 1.85 per cent or less of 4-[(2-hydroxyethyl)amino]-3-nitrophenol under non-oxidising conditions, and in ready to use preparations when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN; and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

4-[(2-HYDROXYETHYL)AMINO]-3-NITROPHENOL

Standard statements: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

4-[(2-HYDROXYETHYL)AMINO]-3-NITROPHENOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The applicant's reasons for the request are:

- 4-[(2-Hydroxyethyl)amino]-3-nitrophenol is reported to be used in permanent and semi-permanent cosmetic hair dye preparations in Australia;
- 4-[(2-Hydroxyethyl)amino]-3-nitrophenol is an extreme skin sensitiser with a local lymph node assay (LLNA) EC3 value (estimated concentration required to produce a three-fold increase in lymphocyte proliferation) of 0.07%;
- 4-[(2-Hydroxyethyl)amino]-3-nitrophenol is a potential developmental toxin;
- There are overseas restrictions and labelling requirements for use of 4-[(2-hydroxyethyl)amino]-3-nitrophenol in hair dyes;
- The existing overseas restrictions are currently under review by the European Commission's Scientific Committee on Consumer Safety (SCCS), to take into account the sensitisation potential of the chemical; and

- When 4-[(2-hydroxyethyl)amino]-3-nitrophenol is used as a hair dye, there is a potential risk of for skin sensitisation, which may be controlled through concentration restrictions and warning labels, as have previously been applied to other sensitising hair dyes considered for inclusion in the SUSMP.

Current scheduling status and relevant scheduling history

4-[(2-Hydroxyethyl)amino]-3-nitrophenol is not currently scheduled and has not been previously considered for scheduling; therefore, scheduling history is not available.

International regulations

The chemical is listed on the following:

- The EU Regulation (EC) No 344/2013 Annex III— List of substances which cosmetic products must not contain except subject to the restrictions laid down: '(a) hair dye substance in oxidative hair dye products; (a) after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 3.0%; (b) hair dye substance in non-oxidative hair dye products; (b) the maximum concentration in ready for use preparation is 1.85%; and for (a) and (b): — do not use with nitrosating agents, — maximum nitrosamine content: 50 µg/kg, — keep in nitrite-free containers' — when concentrations do not exceed the maximum concentration listed in (a) and (b), it must be labelled with the following: hair colourants can cause severe allergic reactions, read and follow instructions.

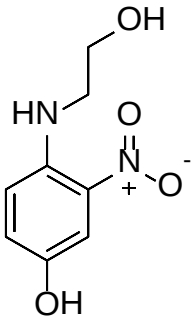
- New Zealand Cosmetic Products Group Standard—Schedule 5: Components cosmetic products must not contain except subject to the restrictions and conditions laid down: '(a) the maximum authorised concentration in the finished cosmetic product as a hair dye substance in non-oxidative hair dye products is 1.85%; (b) in combination with hydrogen peroxide the maximum use concentration upon application is 3.0%; (c) do not use with nitrosating systems; (d) maximum nitrosamine content: 50 µg/kg; and (e) keep in nitrate-free containers'.

- The Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1: List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down: '(a) the maximum authorised concentration in the finished cosmetic product as a hair dye substance in non-oxidative hair dye products is 1.85%; (b) after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 3.0%; (c) do not use with nitrosating systems; (d) maximum nitrosamine content: 50 µg/kg; and (e) keep in nitrate-free containers.'

Substance summary

Table 1.2A: Chemical information

Property	4-[(2-Hydroxyethyl)amino]-3-nitrophenol
CAS No.	65235-31-6
Alternative names	Phenol, 4-[(2-Hydroxyethyl)amino]-3-nitro- (CAS); 3-nitro-*p*-hydroxyethylaminophenol (INCI); 1-hydroxy-3-nitro-4-(ß-hydroxyethyl)-aminobenzene; 3-nitro-4-n-(beta-hydroxyethyl)aminophenol; 4-((2-hydroxyethyl)amino)-3-nitrophenol

Property	4-[(2-Hydroxyethyl)amino]-3-nitrophenol
Chemical structure	
Molecular formula	$C_8H_{10}N_2O_4$
Molecular weight	198.2 g/mol

The following information has been extracted from the NICNAS IMAP Human Health Tier II assessment report for Phenol, 4-[(2-hydroxyethyl)amino]-3-nitro-.[1]

Table 1.2B: Acute toxicity end-points for 4-[(2-hydroxyethyl)amino]-3-nitrophenol

Toxicity	Species	4-((2-hydroxyethyl)amino)-3-nitrophenol	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Sprague Dawley (SD) rats	>2000	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw) No dermal absorption data is available	N/A	No data	N/A
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	N/A	No data	N/A
Skin irritation	New Zealand White Rabbits	Non-irritant at 4 and 6%	N/A
Eye irritation	New Zealand White Rabbits	Slight irritant at 4 and 6%	N/A
Skin sensitisation	CBA/J Mice	Strong sensitiser	Schedule 6

Acute toxicity

4-((2-Hydroxyethyl)amino)-3-nitrophenol is considered to have low acute oral toxicity. The available LD50 of >2000 mg/kg bw supports this conclusion. No data are available for dermal or inhalation toxicity.

[1] Publicly available on the NICNAS website at: https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1799

Irritation

Based on the limited data available, 4-((2-hydroxyethyl)amino)-3-nitrophenol is not considered to be a skin irritant. However, it is considered to be a slight eye irritant:

- In two eye irritation studies 4-((2-hydroxyethyl)amino)-3-nitrophenol was instilled into the conjunctival sacs of New Zealand White rabbits at 4 and 6%, and was reported to be slightly irritating to the eyes based on the observation of slight chemosis and conjunctival redness, which were fully reversed after five days; the observation of folded irises reversed after 48 hours.

Sensitisation

Based on the available data, the chemical is considered to be an extreme skin sensitiser:

- In a local lymph node assay (LLNA) conducted according to OECD TG 429, 4-((2-hydroxyethyl)amino)-3-nitrophenol was applied to the dorsal surface of both ear lobes of female CBA/J mice (4 animals/group) in dimethylformamide once daily for three consecutive days. 4-((2-Hydroxyethyl)amino)-3-nitrophenol, at test concentrations of 0.03, 0.09, 0.28, 0.83 or 2.5%, produced stimulation indices (SI) of 2.18, 3.54, 6.36, 7.61 or 11.22, respectively. The estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated to be 0.07%, indicating extreme skin sensitisation potential.

Repeat-dose toxicity

Apart from developmental effects, 4-((2-hydroxyethyl)amino)-3-nitrophenol is not considered to cause to adverse health effects following repeated oral exposure (NOAEL 200 mg/kg). No data are available for repeated dermal and inhalation toxicity.

Genotoxicity

Based on the weight of evidence from the available *in vitro* and *in vivo* genotoxicity studies, the chemical is not considered to be genotoxic. All *in vivo* genotoxicity test were negative.

Carcinogenicity

No animal toxicity data are available on the carcinogenicity of 4-((2-hydroxyethyl)amino)-3-nitrophenol. Based on the available genotoxicity data, it is not considered to be genotoxic carcinogenic.

Reproduction and developmental toxicity

Limited data are available. The available data indicate that 4-((2-hydroxyethyl)amino)-3-nitrophenol may have potential for developmental toxicity following oral exposure:

- In a prenatal development toxicity study conducted according to OECD TG 414, pregnant SD rats (20 animals/group) were administered 0, 100 or 1000 mg/kg bw/day of 4-((2-hydroxyethyl)amino)-3-nitrophenol daily by oral gavage on gestational days (GDs) 6–15. All rats were euthanised on GD 20. Red discoloured urine was observed in all animals due to the dyeing properties of the chemical. In the 1000 mg/kg bw/day group, the number of viable foetuses was slightly decreased. Two foetuses in this group had malformations including external astomia (congenital absence) of the face and brain, and polydactyly of the digits. External astomia is known to occur spontaneously in rats of this strain at a low incidence and the presence of polydactyly could not be confirmed by a re-examination of the specimen; therefore, the effects were considered as artifactual events. No other adverse effects were observed. The European Commission's Scientific Committee on Consumer Products (SCCP) 2006 Opinion considered 'the no observed adverse effect level (NOAEL) for developmental toxicity to be 100 mg/kg/day and the NOAEL for maternal toxicity 1000 mg/kg/day, which suggests that teratogenic (external astomia) and embryotoxic (decreased number of live foetuses) effects occurred at dose levels which were not toxic to the pregnant dams.

Public exposure

4-((2-Hydroxyethyl)amino)-3-nitrophenol is reported to be used in permanent and semi-permanent hair dye preparations in Australia.

Pre-meeting public submissions

One (1) pre-meeting submission was received in support. The main points were that the new schedule entry would be in alignment with international regulators in the EU, ASEAN and NZ.

Summary of ACCS advice to the delegate

The committee advised that 4-((2-hydroxyethyl)amino)-3-nitrophenol be entered in Schedule 6 as the INCI name, 3-nitro-*p*-hydroxyethylaminophenol, in the Poisons Standard as follows:

Schedule 6 - New Entry

3-NITRO-*p*-HYDROXYETHYLAMINOPHENOL **except**:

a) in non-oxidative hair dye preparations containing 1.85 per cent or less of 3-nitro-*p*-hydroxyethylaminophenol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

Written in letters not less than 1.5 mm in height; or

b) in oxidative hair dye preparations containing 3 per cent or less of 3-nitro-*p*-hydroxyethylaminophenol after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

Written in letters not less than 1.5 mm in height.

The committee also recommended appendix and index entries be created as follows:

Appendix F, Part 3 – New Entry

3-NITRO-*p*-HYDROXYETHYLAMINOPHENOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

Index - New Entry

3-NITRO-*p*-HYDROXYETHYLAMINOPHENOL
cross reference: 4-[(2-hydroxyethyl)amino]-3-nitrophenol

Schedule 6
Appendix F, Part 3

The committee also advised an implementation date of **1 June 2017**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (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 comprised the following:

- 3-Nitro-*p*-hydroxyethylaminophenol is used in hair dyes, and dermal contact is unavoidable.
- 3-Nitro-*p*-hydroxyethylaminophenol is an extreme skin sensitiser, and meets the factors for Schedule 6.
- The risk of skin sensitisation when exposed to 3-nitro-*p*-hydroxyethylaminophenol can be managed with mandatory warning statements and concentration cut-offs for hair dye products to be exempted from Schedule 6 .

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submission received
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is to create a new Schedule 6 entry for 4-((2-hydroxyethyl)amino)-3-nitrophenol under the INCI name, 3-nitro-*p*-hydroxyethylaminophenol.

The wording for the schedule, appendix and index entries are as follows:

Schedule 6 - New Entry

3-NITRO-*p*-HYDROXYETHYLAMINOPHENOL **except**:

a) in non-oxidative hair dye preparations containing 1.85 per cent or less of 3-nitro-*p*-hydroxyethylaminophenol when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

Written in letters not less than 1.5 mm in height; or

b) in oxidative hair dye preparations containing 3 per cent or less of 3-nitro-*p*-hydroxyethylaminophenol after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions

should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

Written in letters not less than 1.5 mm in height.

Appendix F, Part 3 – New Entry

3-NITRO-*p*-HYDROXYETHYLAMINOPHENOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

Index - New Entry

3-NITRO-*p*-HYDROXYETHYLAMINOPHENOL
cross reference: 4-[(2-hydroxyethyl)amino]-3-nitrophenol

Schedule 6
Appendix F, Part 3

The proposed implementation date is **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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 interim decision are the following:

- The delegate acknowledges the committee's advice.
- 3-Nitro-*p*-hydroxyethylaminophenol is used in hair dyes, and dermal contact is unavoidable.
- 3-Nitro-*p*-hydroxyethylaminophenol is an extreme skin sensitiser, and meets the factors for Schedule 6.
- The risk of skin sensitisation when exposed to 3-nitro-*p*-hydroxyethylaminophenol can be managed with mandatory warning statements and concentration cut-offs for hair dye products to be exempted from Schedule 6.

Public submissions on the interim decision

One (1) submission was received which supported the delegate's interim decision with amendments. The main point in support was that the proposed schedule entry would be in alignment with international regulations in the EU. The main points were:

- No Appendix E Standard Statements are proposed. The submission suggests that Standard Statements should be applied in a way that is consistent with other existing entries for scheduled hair dye substances.
- The submission questions the use of the warning statement, '*This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye'* and whether the reason for its inclusion is eye irritancy or sensitisation.
- The appropriateness of the proposed 'earliest possible implementation date' of 1 June 2017. The submission stresses that an adequate transition period of at least 12 months must be allowed for any labelling changes and/or reformulation that may be required where no immediate risk has been identified; and that there is no evidence to suggest immediate action is required for the risk management of this substance.

Delegate's final decision

The delegate's final decision is to create new Schedule 6, Appendices E & F and Index entries for 4-((2-hydroxyethyl)amino)-3-nitrophenol under the INCI name, 3-nitro-p-hydroxyethylaminophenol as follows:

Schedule 6 - New Entry

3-NITRO-*p*-HYDROXYETHYLAMINOPHENOL **except**:

a) in non-oxidative hair dye preparations containing 1.85 per cent or less of 3-nitro-*p*-hydroxyethylaminophenol after mixing when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and
WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and
Written in letters not less than 1.5 mm in height; or

b) in oxidative hair dye preparations containing 3 per cent or less of 3-nitro-*p*-hydroxyethylaminophenol after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and
WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and
Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

3-NITRO-*p*-HYDROXYETHYLAMINOPHENOL

Standard statement: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

3-NITRO-*p*-HYDROXYETHYLAMINOPHENOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

Index - New Entry

3-NITRO-*p*-HYDROXYETHYLAMINOPHENOL
cross reference: 4-[(2-hydroxyethyl)amino]-3-nitrophenol

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

The implementation date has been extended to **1 February 2018.**

The delegate confirms that the reasons for the final decision are the same as those provided from the interim decision. Additional reasons for the final decision include:

- The warning statement '*This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye'* has been included as the chemical is a slight eye irritant at concentrations 4 and 6% and likely to be irritating at exempted concentrations when used in hair dye preparations.

- Appendix E Standard Statements apply to the scheduled substance and not the exemptions (as specified in a) and b) of the Schedule 6 entry for 3-nitro-p-hydroxyethylaminophenol)). 3-Nitro-p-hydroxyethylaminophenol is a slight eye irritant at 4 and 6% which is likely to become more severe at higher concentrations; therefore Standard Statement E1 (if in eyes wash out immediately with water) is appropriate.
- The words *'after mixing'* have been added to the schedule entry for clarity
- The delegate notes that a longer implementation time is required to allow for labelling changes and/or reformulation.

1.3 Hydroxyethyl-3,4-methylenedioxyaniline

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new Schedule 6 entry for hydroxyethyl-3,4-methylenedioxyaniline and its hydrochloride salt in hair dyes and eyebrow/eyelash colouring products and to determine whether appropriate exemption cut-off and labelling is required.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 6 – New Entry

HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE AND ITS HYDROCHLORIDE **except** in hair dye preparations containing 1.5 per cent or less of hydroxyethyl-3,4-methylenedioxyaniline or its hydrochloride under oxidising conditions (after mixing with hydrogen peroxide), and when the immediate container and primary pack are labelled with the following statement:

KEEP OUT OF REACH OF CHILDREN; and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals, and when used for eyelash or eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5mm in height.

Appendix E, Part 2 – New Entry

HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE AND ITS HYDROCHLORIDE

Standard statements: A [for advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once).], E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE AND ITS HYDROCHLORIDE

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The applicant's reasons for the request are:

- The hydrochloride salt of hydroxyethyl-3,4-methylenedioxyaniline has reported cosmetic use in permanent and semi-permanent hair dye preparations in Australia. Overseas, the hydrochloride salt is used in oxidative hair dye products that are potentially available for use in Australia.
- Existing overseas restrictions for use of the hydrochloride salt of hydroxyethyl-3,4-methylenedioxyaniline in hair dyes where the maximum concentration allowed in the finished cosmetic product as a hair dye substance in oxidative hair dye products is 1.5%.

- The chemicals are secondary amines and thus prone to nitrosation, and should not be used in combination with nitrosating substances; the maximum nitrosamine content should be less than 50 ppb and should be kept in nitrite-free containers for the hydrochloride salt.
- The hydrochloride salt of hydroxyethyl-3,4-methylenedioxyaniline is a strong skin sensitiser and has moderate systemic acute oral toxicity.
- The risk could be controlled by including warning statements and first aid instructions on labels for hair dye formulations containing the chemicals.
- Many countries, including those in the European Union (EU), have restricted the use of the hydrochloride salt in cosmetics (refer to International Regulations, page 4).
- When hydroxyethyl-3,4-methylenedioxyaniline and its hydrochloride are used as hair dyes, there is a potential risk of for skin sensitisation, which may be controlled through concentration restrictions and warning labels, as have previously been applied to other sensitising hair dyes considered for inclusion in the SUSMP.

Current scheduling status and relevant scheduling history

Hydroxyethyl-3,4-methylenedioxyaniline and its hydrochloride salt are not currently scheduled and have not been previously considered for scheduling; therefore, a scheduling history is not available.

International regulations

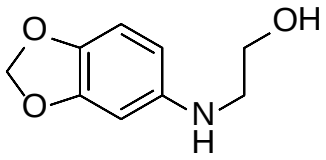
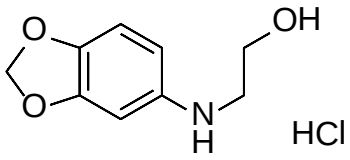
The following restrictions are reported for the chemical. Similar restrictions to those in the European Union (EU) Cosmetics Directive apply to all jurisdictions:

- The EU Cosmetics Regulation No 1223/2009 Annex III—List of substances provisionally allowed in cosmetic products with restriction stated as 'after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 1.5%: do not use with nitrosating agents, maximum nitrosamine content 50 microgram/kg, and keep in nitrite-free containers' . There is a requirement to label products containing these chemicals at lower concentrations as potentially sensitising.
- The Association of South East Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1 List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down. The restriction is stated as ‘after mixing under oxidative conditions the maximum concentration applied to hair must not exceed 1.5%; Do not use with nitrosating systems; Maximum nitrosamine content: 50 µg/kg; Keep in nitrite-free containers’.
- The New Zealand (NZ) Cosmetic Products Group Standard—Schedule 5, Table 1 Components cosmetic products must not contain except subject to restrictions and conditions laid down. The restriction is stated as ‘in combination with hydrogen peroxide the maximum use concentration upon application is; 1.5%; Do not use with nitrosating systems; Maximum nitrosamine content: 50 µg/kg; Keep in nitrite-free containers’.

Substance summary

Table 1.3A: Chemical information

Property	Hydroxyethyl-3,4-methylenedioxyaniline	Hydroxyethyl-3,4-methylenedioxyaniline hydrochloride
CAS names	Ethanol, 2-(1,3-benzodioxol-5-ylamino)-	Ethanol, 2-(1,3-benzodioxol-5-ylamino)-, hydrochloride
CAS numbers	81329-90-0	94158-14-2

Property	Hydroxyethyl-3,4-methylenedioxyaniline	Hydroxyethyl-3,4-methylenedioxyaniline hydrochloride
IUPAC and/or common and/or other names	Hydroxyethyl-3,4-methylenedioxyaniline	Hydroxyethyl-3,4-methylenedioxyaniline HCl (INCI)
Chemical structure		
Molecular formula	$C_9H_{12}ClNO_3$	$C_9H_{12}ClNO_3$
Molecular weight	217.649 g/mol	217.6 g/mol

The following toxicology information was extracted from the NICNAS IMAP Human Health Tier II assessment for Ethanol, 2-(1,3-benzodioxol-5-ylamino)-, hydrochloride.[2] Further information can also be found in the European Commission Scientific Committee on Consumer Safety (SCCS) report for hydroxyethyl-3,4-methylenedioxyaniline hydrochloride.[3]

Table 1.3B: Acute toxicity end-points for hydroxyethyl-3,4-methylenedioxyaniline hydrochloride

Toxicity	Species	Hydroxyethyl-3,4-methylenedioxyaniline HCl	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	1550 (male); 1650 (female)	Schedule 6
	Mouse	850 (female)	
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	N/A
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	No data	N/A
Skin irritation	Guinea pig	Not irritating at 5% concentration	N/A
Eye irritation	Guinea pig	Transiently irritating at 2% concentration	N/A
Skin sensitisation (LLNA)	Mouse	Skin sensitiser (calculated EC3<0.5%)	Schedule 6

A short summary of the toxicity, exposure, use, international risk management control of hydroxyethyl-3,4-methylenedioxyaniline HCl are included below. For further information, please see assessment report.

[2] Publicly available on the NICNAS website at: https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1797

[3] Publicly available at: http://ec.europa.eu/health//sites/health/files/scientific_committees/consumer_safety/docs/sccs_o_006.pdf

Acute toxicity

The hydrochloride salt of hydroxyethyl-3,4-methylenedioxyaniline has moderate acute oral toxicity in male and female rats and in female mice. There are no data on acute dermal and inhalation toxicity.

Irritation

Limited data are available in guinea pigs. Hydroxyethyl-3,4-methylenedioxyaniline HCl at a 5% concentration is not irritating to the skin. Hydroxyethyl-3,4-methylenedioxyaniline HCl at a 2% concentration is transiently irritating to the eyes.

Sensitisation

In a local lymph node assay (LLNA) conducted according to the OECD TG 429. Hydroxyethyl-3,4-methylenedioxyaniline HCl, at dilutions of 0.5, 1.5, 5 or 10%, was applied to the ears of female CBA/J mice (5/group) for three consecutive days. Two separate vehicles were used, dimethyl sulfoxide (DMSO) or in a mixture (3:3:1) of water/acetone/olive oil (equal to the maximum solubility). For the DMSO vehicle, the mean stimulation indices (SIs) were dose-dependent at 6.4, 5.0, 8.0 and 12.4 for the 0.5, 1.5, 5 and 10% dilutions, respectively. For the other vehicle (water/acetone/olive oil), the SIs were 4.3, 3.6, 3.3 and 4.4 for the 0.5, 1.5, 5 and 10% dilutions, respectively. The estimated concentration (EC) needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated to be <0.5%, indicating strong sensitising potential (SCCS, 2009).

Repeat-dose toxicity

Based on a 90-day study in rats, hydroxyethyl-3,4-methylenedioxyaniline HCl is not expected to cause serious damage to health from repeated oral exposure.

Mutagenicity and Genotoxicity

Based on the available data from in vitro and in vivo genotoxicity studies, hydroxyethyl-3,4-methylenedioxyaniline HCl is not considered to be genotoxic.

Carcinogenicity

No data were available for carcinogenicity.

Reproduction and developmental toxicity

Based on the available data, hydroxyethyl-3,4-methylenedioxyaniline HCl is not expected to have reproductive or developmental toxicity. Foetal effects observed in the animals at high doses are considered secondary to maternal toxicity

Pre-meeting public submissions

One (1) pre-meeting submission was received in support. The main points were that the new schedule entry would be in alignment with international regulators in the EU, ASEAN and NZ.

Summary of ACCS advice to the delegate

The committee advised that hydroxyethyl-3,4-methylenedioxyaniline be entered in Schedule 6 in the Poisons Standard, with an exemption cut-off of 1.5% as follows:

Schedule 6—New Entry

HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE (including its salts) **except** in oxidative hair dye preparations containing 1.5 per cent or less of hydroxyethyl-3,4-methylenedioxyaniline after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made

before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

Written in letters not less than 1.5 mm in height.

The committee also advised that appendix entries be created as follows:

Appendix E, Part 2 – New Entry

HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE

Standard statements: E1 (if in eyes wash out immediately with water), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – New Entry

HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The committee recommended an implementation date of **1 June 2017**.

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

The reasons for the advice comprised the following:

- Hydroxyethyl-3,4-methylenedioxyaniline is used in permanent hair dye preparations in Australia.
- Hydroxyethyl-3,4-methylenedioxyaniline and its salt are strong skin sensitisers and have moderate systemic acute oral toxicity consistent with Schedule 6 factors.
- Hydroxyethyl-3,4-methylenedioxyaniline and its salt are secondary amines and thus prone to nitrosation.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is to create a new Schedule 6 entry for hydroxyethyl-3,4-methylenedioxyaniline, with an exemption cut-off of 1.5 per cent.

The proposed wording for the schedule and appendix entries is as follows:

Schedule 6 – New Entry

HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE (including its salts) **except** in oxidative hair dye preparations containing 1.5 per cent or less of hydroxyethyl-3,4-methylenedioxyaniline after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE

Standard statements: E1 (if in eyes wash out immediately with water), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – New Entry

HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The proposed implementation date is **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; and (c) the toxicity of a substance.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Hydroxyethyl-3,4-methylenedioxyaniline is used in permanent hair dye preparations in Australia.
- Hydroxyethyl-3,4-methylenedioxyaniline and its salt are strong skin sensitisers and have moderate systemic acute oral toxicity consistent with Schedule 6 factors.
- Hydroxyethyl-3,4-methylenedioxyaniline and its salt are secondary amines and thus prone to nitrosation.

Public submissions on the interim decision

One (1) submission was received which supported the delegate's interim decision with amendments. The main point in support was that the proposed schedule entry would be in alignment with international regulations in the EU. The main points were:

- No Appendix E Standard Statements are proposed. The submission suggests that Standard Statements should be applied in a way that is consistent with other existing entries for scheduled hair dye substances.
- The submission questions the use of the warning statement, '*This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye'* and whether the reason for its inclusion is eye irritancy or sensitisation.
- The appropriateness of the proposed 'earliest possible implementation date' of 1 June 2017. The submission stresses that an adequate transition period of at least 12 months must be allowed for any labelling changes and/or reformulation that may be required where no immediate risk has been identified; and that there is no evidence to suggest immediate action is required for the risk management of this substance.

Delegate's final decision

The delegate's final decision is to create new Schedule 6 and Appendices E & F entries for hydroxyethyl-3,4-methylenedioxyaniline as follows:

Schedule 6 – New Entry

HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE (including its salts) **except** in oxidative hair dye preparations containing 1.5 per cent or less of hydroxyethyl-3,4-methylenedioxyaniline after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE

Standard statements: E1 (if in eyes wash out immediately with water), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – New Entry

HYDROXYETHYL-3,4-METHYLENEDIOXYANILINE

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The implementation date has been extended to **1 February 2018.**

The delegate confirms that the reasons for the final decision are the same as those provided from the interim decision. Additional reasons for the final decision include:

- The warning statement '*This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye'* has been included as the chemical is transiently irritating to the eyes at 2%; it expect to be irritating at concentrations of hydroxyethyl-3,4-methylenedioxyaniline used in hair dyes (1.5% and less).
- Appendix E Standard Statements apply to the scheduled substance and not the exemptions (hydroxyethyl-3,4-methylenedioxyaniline at 1.5% in oxidative hair dye preparations is exempt from scheduling). Hydroxyethyl-3,4-methylenedioxyaniline is a strong skin sensitiser (EC3<0.5%); therefore Standard Statement S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water) is appropriate.
- The delegate notes that a longer implementation time is required to allow for labelling changes and/or reformulation.

1.4 1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new Schedule 6 entry for 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride in hair dyes and eyebrow/eyelash colouring products and to determine whether an appropriate exemption cut-off is required.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 6 – New entry

1,3-BIS(2,4-DIAMINOPHENOXY)PROPANE TETRAHYDROCHLORIDE **except** when used in hair dye colouring products at a concentration of 1.8 per cent or less of 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride, or 1.2 per cent or less of 1,3-bis(2,4-diaminophenoxy)propane (the free base), and when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN; and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5mm in height.

Appendix E, Part 2 – New Entry

1,3-BIS(2,4-DIAMINOPHENOXY)PROPANE TETRAHYDROCHLORIDE

Standard statements: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

1,3-BIS(2,4-DIAMINOPHENOXY)PROPANE TETRAHYDROCHLORIDE

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The applicant's reasons for the request are:

- 1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride is an eye irritant; a moderate skin sensitiser with a local lymph node assay (LLNA) EC3 value of 14.7%.
- 1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride has existing overseas restrictions, including a maximum allowable concentration of 1.8% in cosmetics, with warnings of sensitisation at lower concentrations, in the European Union (EU).

Current scheduling status and relevant scheduling history

1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride is not currently scheduled and has not been previously considered for scheduling; therefore, scheduling history is not available. There is however, a derivative of 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride, 1,3-benzenediamine that is currently listed in the SUSMP in Schedule 10 as follows:

Schedule 10

1,3-BENZENEDIAMINE in preparations for cosmetic use and skin colouration (including tattooing).

Australian regulatory information

The chemical is reported to be used in permanent hair dye preparations in Australia. Currently, there are no restrictions in Australia on using this chemical in cosmetics/hair dyes or eyelash colouring products. In the absence of any regulatory controls, the characterised critical health effects (skin sensitisation) have the potential to pose an unreasonable risk to the public under the uses identified.

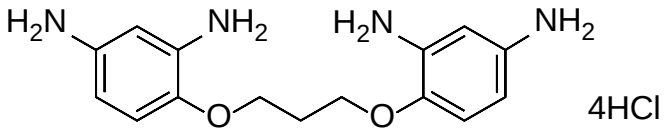
International regulations

The chemical is listed on the following:

- EU Cosmetics Regulation 1223/2009 Annex III—List of substances which cosmetic products must not contain except subject to the restrictions laid down: maximum concentration in cosmetic formulation must not exceed 1.2 % calculated as free base (1.8 % as tetrahydrochloride salt). The Cosmetics Regulation also mandates label warning statements relating to the sensitisation potential of the chemical;
- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1—List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down; and
- New Zealand Cosmetic Products Group Standard—Schedule 5—Table 1: Components cosmetic products must not contain except subject to the restrictions and conditions laid down.

Substance summary

Table 1.4A: Chemical information

Property	1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride
CAS No.	74918-21-1
Chemical structure	
Molecular formula	$C_{15}H_{24}Cl_4N_4O_2$
Molecular weight	434.2 g/mol
Alternative names	1,3-Bis-(2,4-Daiminophenoxy)propane HCL (INCI); 1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride (CAS); 1,3-Benzenediamine, 4,4'-[1,3-propanediylbis(oxy)]bis-, tetrahydrochloride

The following toxicology information was extracted from the NICNAS IMAP Human Health Tier II assessment.[4] Further information can also be found in the European Commission Scientific Committee on Consumer Products (SCCP) report.[5]

[4] Publicly available on the NICNAS website at" https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1794

[5] Publicly available at http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_105.pdf. This report incorrectly identifies a synonym of 1,3-bis(2,4-diaminophenoxy)propane tetra hydrochloride to be HC Blue 16.

Table 1.4B: Acute toxicity end-points for 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride

Toxicity	Species	1,3-bis(2,4-diaminophenoxy)propane tetra hydrochloride	SPF (2015) Classification
Acute oral toxicity median lethal dose (LD_{50}) (mg/kg bodyweight (bw))	Wistar rat	3570	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	N/A
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	N/A	No data	N/A
Skin irritation	New Zealand White rabbits	Mild skin irritant	Schedule 5
Eye irritation	New Zealand White rabbits	Moderate eye irritation	Schedule 5
Skin sensitisation (LLNA)	CBA/J mice	The chemical is a moderate skin sensitiser (EC3 value of 14.7%)	Schedule 6

Acute toxicity

1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride has low acute toxicity based on results from animal tests following oral exposure. The LD_{50} in rats is 3570 mg/kg bw.

1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride was assessed in a non-guideline acute oral toxicity study in male Wistar rats (10 animals/group). The animals were dosed by oral gavage at 2510, 3160, 3570, 3980 or 5010 mg/kg bw. Animals were observed for 14 days. Mortalities occurred in the groups as follows: 0/10 (2510 mg/kg bw), 2/10 (3160 mg/kg bw), 5/10 (3570 mg/kg bw), 8/10 (3980 mg/kg bw), and 9/10 (5010 mg/kg bw). An LD50 of 3570 mg/kg bw was determined from this study.

Skin irritation

1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride was reported in a study to cause mild, transient skin irritation in New Zealand White rabbits:

- In an OECD TG 404 (acute dermal irritation/corrosion) study, 0.5 g of the moistened substance was applied to the intact, shaved back skin of three New Zealand White rabbits. The test chemical was left in place for four hours under a semi-occlusive patch. The application resulted in slight erythema on the exposed skin of all rabbits at one hour after treatment. No oedema was observed and no evidence of irreversible damage was apparent. Under these test conditions, 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride caused minimal and transient irritation of the skin.

Eye irritation

1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride was reported to irritate the eyes when tested according to OECD TG 405 (acute eye irritation/corrosion). The average corneal, iridial, conjunctival redness and conjunctival chemosis scores were given as (1/1/3/4). The effects were reversible within 14 days of application.

In a study conducted according to OECD TG 405, 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride (approximately 45.2 mg as an undiluted solution) was instilled into the conjunctival sac of one eye each of three New Zealand White rabbits and left for 24 hours. The chemical caused corneal injury including opacity (maximum grade 1 in all animals up to 72 hours after instillation) and epithelial damage (maximum 65% of the corneal surface, 24 hours after instillation). Corneal injury resolved within 72 hours. Iridial irritation (grade 1) was observed in all animals but resolved during the observation period. Conjunctival irritation consisted of redness (up to grade 3), chemosis (up to grade 4) and discharge (up to grade 2) and had completely resolved in one animal within seven days and in the other animals within 14 days. No mortalities or evidence of systemic toxicity were observed. Under the conditions of the study, the test substance was irritating to rabbit eyes.

Sensitisation

1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride is considered to be a moderate skin sensitiser based on the positive results seen in a single LLNA. The EC3 (estimated concentration required to produce a three-fold increase in lymphocyte proliferation) was 14.7%.

The potential for 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride to promote sensitisation was investigated in a study conducted according to OECD TG 429 (skin sensitisation: local lymph node assay). Female CBA/J mice (five animals/group) were topically administered the chemical in solution on the dorsal surface of each ear lobe once daily, for three consecutive days at 5, 25 and 50% (in ethanol/water mixture (7/3, volume/volume)). The rate of radio-labelled thymidine incorporation in the lymph nodes was used to calculate stimulation indices. Even at the highest concentration, no local effects were observed on the skin of the ears. The SI for the different dose groups were 1.2 ± 1.0 (5%), 4.9 ± 1.1 (25%) and 4.3 ± 1.0 (50%), respectively. An EC3 value of 14.7% was calculated. On the basis of this finding, the test chemical is considered to be a skin sensitiser.

Oral repeat-dose toxicity

In a 90-day oral gavage study in rats, a no observed adverse effect level (NOAEL) of 40 mg/kg bw/day was reported.

- 1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride was assessed for toxicity following repeated oral dosing in a study conducted according to OECD TG 408 (repeated dose 90-day oral toxicity study in rodents). Crl:(WI)BR Wistar rats (12 animals/sex/group) were dosed with the chemical by gavage for 13 weeks at 0, 40, 130 or 360 mg/kg bw/day. Discolouration and brown staining was evident in several tissues in the high dose group. Some ocular pathology was evident in the mid and high dose groups. Reduced weight gain was also evident in high dose males. The mid and high dose groups also exhibited significant changes in organ weights (thymus, adrenal glands, spleen and kidneys). Some cardiac degeneration was evident in the mid and high dose groups. Two mortalities were recorded in the two highest dose groups; however, evaluation at necropsy showed no clear cause of death. Minor haematological changes were reported for the low dose group; however, these were not considered adverse effects associated with treatment. There were no treatment-related changes in food consumption in any group. On the basis of these findings, an NOAEL of 40 mg/kg bw/day was established.

Genotoxicity

Based on the weight of evidence from the available *in vitro* and *in vivo* genotoxicity studies, 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride is not considered to be genotoxic. All *in vivo* genotoxicity tests were negative.

Reproduction and developmental toxicity

Based on the results, a reported NOAEL of 180 mg/kg bw/day was determined for maternal and foetal toxicity.

- In a non-guideline study, female Sprague Dawley rats (21 animals/group) were administered the chemical by oral gavage on gestation days 6–15, at 0, 20, 60 or 180 mg/kg bw/day. No maternal deaths occurred during the study and dams did not exhibit any evidence of a toxic response to the

test chemical at any dose. There was no evidence that the test chemical had any influence on the outcome of pregnancy. Resorption rates and post-implantation losses were not affected by treatment. No foetal effects of treatment were observed. On the basis of these findings, an NOAEL of 180 mg/kg bw/day, was determined for foetal and maternal toxicity.

Pre-meeting public submissions

One (1) pre-meeting submission was received in support. The main points were that the new schedule entry would be in alignment with international regulators in the EU, ASEAN and NZ.

Summary of ACCS advice to the delegate

The committee advised that a new Schedule 6 entry for 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride be created under the common name, HC Blue 16,[6] with an exemption cut-off of 1.2% in the Poisons Standard as follows:

Schedule 6 – New entry

HC BLUE 16 (including its salts) **except** when in hair dye preparations containing 1.2 per cent or less of HC Blue 16 when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

Written in letters not less than 1.5 mm in height.

The committee also advised that appendix and index entries be created as follows:

Appendix E, Part 2 – New Entry

HC BLUE 16

Standard statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), E1 (if in eyes wash out immediately with water), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – New Entry

HC BLUE 16

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation), 79 (Will irritate eyes).
Safety directions: 1 (Avoid contact with eyes).

Index – New entry

HC BLUE 16
cross reference: 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride

[6] The committee recommended that the name of the schedule entry should be the common name, HC BLUE 16 (identified as a synonym of 1,3-bis(2,4-diaminophenoxy)propane tetra hydrochloride in the Scientific Committee on Consumer Products report (2007)). However, a public submission in response to the interim decision has indicated that HC Blue 16 does not refer to 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride (CAS No. 74918-21-1) but refers to a different chemical, *N,N*-dimethyl-3-{[4-(methylamino)-9,10-dioxo-9,10-dihydro-1-anthracenyl] amino}-*N*-propyl-1-propanaminium bromide (CAS No. 502453-61-4).

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

The committee recommended an implementation date of **1 June 2017**.

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

The reasons for the advice comprised the following:

- As a cosmetic in many other countries, Australian consumers will also have access to the effective cosmetic, 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride;
- While the risk of skin sensitisation is real, the risk is attenuated by the consumer product being available in low strength, and the consumer product being labelled appropriately to warn consumers of skin sensitisation risk;
- 1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride is used as a precursor for hair care products, including hair dyes. Such products may be used widely;
- 1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride is uses in hair dyes, and dermal contact is unavoidable;
- 1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride has a moderate skin sensitisation potential, which is consistent with Schedule 6 factors;
- 1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride should only be exempt from Schedule 6 at a lower concentration of 1.2% of the free base, and when it is labelled with appropriate warnings regarding skin sensitisation; and
- Placing scheduling restrictions on 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride would align Australian standards with those in other developed economies.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is to create a new Schedule 6 entry for 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride under the common name, HC Blue 16, [7] with an exemption cut-off of 1.2 per cent.

[7] A public submission in response to the interim decision has indicated that HC Blue 16 does not refer to 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride (CAS No. 74918-21-1) but refers to a different chemical, *N,N*-dimethyl-3-{[4-(methylamino)-9,10-dioxo-9,10-dihydro-1-anthracenyl] amino}-*N*-propyl-1-propanaminium bromide (CAS No. 502453-61-4).

The wording for the schedule, appendix and index entries are as follows:

Schedule 6 – New entry

HC BLUE 16 (including its salts) **except** when in hair dye preparations containing 1.2 per cent or less of HC Blue 16 when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

HC BLUE 16

Standard statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)), E1 (if in eyes wash out immediately with water), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – New Entry

HC BLUE 16

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation), 79 (Will irritate eyes).
Safety directions: 1 (Avoid contact with eyes).

Index – New entry

HC BLUE 16
cross reference: 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride

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

The proposed implementation date is **1 June 2017**.

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

The reasons for the interim decision were the following:

- The delegate acknowledges the committee's advice.
- As a cosmetic in many other countries, Australian consumers will also have access to the effective cosmetic, 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride ;
- While the risk of skin sensitisation is real, the risk is attenuated by the consumer product being available in low strength, and the consumer product being labelled appropriately to warn consumers of skin sensitisation risk;

- 1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride is used as a precursor for hair care products, including hair dyes. Such products may be used widely;
- 1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride is used in hair dyes, and dermal contact is unavoidable;
- 1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride has a moderate skin sensitisation potential, which is consistent with Schedule 6 factors;
- 1,3-Bis(2,4-diaminophenoxy)propane tetrahydrochloride should only be exempt from Schedule 6 at a lower concentration of 1.2% of the free base, and when it is labelled with appropriate warnings regarding skin sensitisation; and
- Placing scheduling restrictions on 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride would align Australian standards with those in other developed economies.

Public submissions on the interim decision

One (1) submission was received which supported the delegate's interim decision with amendments. The main point in support was that the proposed schedule entry would be in alignment with international regulations in the EU. The main points were:

- The incorrect synonym of HC Blue 16 has been included for 1,3-bis(2,4-diaminophenoxy) propane tetrahydrochloride (CAS number 74918-21-1). The submission asserts that HC Blue 16 is a different chemical (N,N-dimethyl-3-{[4-(methylamino)-9,10-dioxo-9,10-dihydro-1-anthracenyl] amino}-N-propyl-1-propanaminium bromide, CAS number 502453-61-4).
- No Appendix E Standard Statements are proposed. The submission suggests that Standard Statements should be applied in a way that is consistent with other existing entries for scheduled hair dye substances.
- The submission questions the use of the warning statement, '*This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye'* and whether the reason for its inclusion is eye irritancy or sensitisation.
- The appropriateness of the proposed 'earliest possible implementation date' of 1 June 2017. The submission stresses that an adequate transition period of at least 12 months must be allowed for any labelling changes and/or reformulation that may be required where no immediate risk has been identified; and that there is no evidence to suggest immediate action is required for the risk management of this substance.

Delegate's final decision

The delegate's final decision is to create new Schedule 6, Appendices E & F and Index entries for 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride as follows:

Schedule 6 – New entry

1,3-BIS(2,4-DIAMINOPHENOXY)PROPANE (including its salts) **except** when in hair dye preparations containing 1.2 per cent or less of 1,3-bis(2,4-diaminophenoxy)propane after mixing when the immediate container and primary pack are labelled with the following statements:

> KEEP OUT OF REACH OF CHILDREN, and
>
> WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and
>
> Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

1,3-BIS(2,4-DIAMINOPHENOXY)PROPANE

Standard statements: E1 (if in eyes wash out immediately with water), S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water).

Appendix F, Part 3 – New Entry

1,3-BIS(2,4-DIAMINOPHENOXY)PROPANE

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation), 79 (Will irritate eyes).
Safety directions: 1 (Avoid contact with eyes).

Index – New entry

1,3-BIS(2,4-DIAMINOPHENOXY)PROPANE

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

The implementation date has been extended to **1 February 2018.**

The delegate confirms that the reasons for the final decision are the same as those provided from the interim decision. Additional reasons for the final decision include:

- The delegate notes that HC Blue 16 is not an alternative name for 1,3-bis(2,4-diaminophenoxy)propane tetrahydrochloride (74918-21-1) but refers to different, unrelated chemical (*N,N*-dimethyl-3-{[4-(methylamino)-9,10-dioxo-9,10-dihydro-1-anthracenyl]amino}-*N*-propyl-1-propanaminium bromide, CAS No 502453-61-4). The wording of the Schedule entry has been amended to reflect this.
- The warning statement 'This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye' has been included as the chemical is a moderate eye irritant.
- Appendix E Standard Statements apply to the scheduled substance and not the exemptions (1,3-bis(2,4-diaminophenoxy)propane at 1.2% in hair dye preparations is exempt from scheduling). 1,3-Bis(2,4-diaminophenoxy)propane is a moderate skin sensitiser; therefore Standard Statement S1 (If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water) is appropriate.
- Standard Statement A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)) is not appropriate as this chemical has low acute oral toxicity.
- The words *'after mixing*' have been added to the schedule entry for clarity
- The delegate notes that a longer implementation time is required to allow for labelling changes and/or reformulation.

1.5 2,2'-[(4-Amino-3-nitrophenyl)imino]bisethanol and its monohydrochloride

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new Schedule 6 entry for 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol and its monohydrochloride in hair dyes and eyebrow/eyelash colouring products and to determine whether an appropriate exemption cut-off is required.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 6 – New Entry

2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL **except** when used in hair dye preparations containing 1.25 per cent or less of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol or its monohydrate under oxidative conditions (after mixing with hydrogen peroxide), or 2.5 per cent of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol or its monohydrate under non-oxidative conditions, and when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN; and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5mm in height.

Appendix E, Part 2 – New Entry

2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL AND ITS MONOHYDROCHLORIDE

Standard statements: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL AND ITS MONOHYDROCHLORIDE

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The applicant's reasons for the request are:

- The 2,2'-((4-amino-3-nitrophenyl)imino)bisethanol hydrochloride salt is reported to be used in semi-permanent hair dye preparations in Australia.
- Both the free based and the salt have reported cosmetic uses overseas, as hair dye substances in oxidative (permanent) and non-oxidative (semi-permanent) hair dye products, that are potentially available for use in Australia.
- The chemicals are moderate skin sensitisers.
- Existing overseas restrictions for use of the chemicals in hair dyes where the maximum concentration allowed in the finished cosmetic product as a hair dye substance in non-oxidative hair dye products is 2.5% and the maximum use concentration upon application is 1.25% (after mixing under oxidative conditions), with labelling requirements at lower concentrations.
- The risk could be controlled by including warning statements on labels for hair dye formulations containing the chemicals at any concentration.
- When 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol and its monohydrochloride are used as hair dyes, there is a potential risk of for skin sensitisation, which may be controlled through concentration restrictions and warning labels, as have previously been applied to other sensitising hair dyes considered for inclusion in the SUSMP.

Current scheduling status and relevant scheduling history

2,2'-[(4-Amino-3-nitrophenyl)imino]bisethanol and its monohydrochloride (HC Red 13) are not currently scheduled and have not been previously considered for scheduling; therefore, scheduling history is not available.

Australian regulatory history

The salt of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol is reported to be used in semi-permanent hair dye preparations in Australia. Currently, there are no restrictions in Australia for using these chemicals in cosmetic products.

International regulations

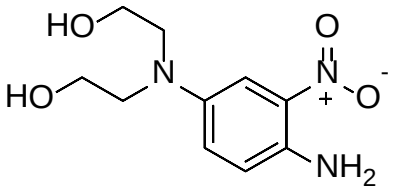
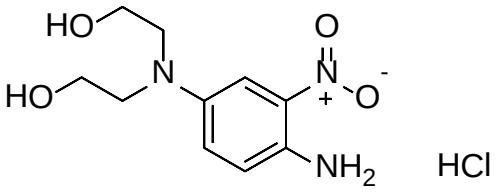
The use of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol and its salt as cosmetics in the European Union (EU) is subject to the restrictions described in the EU Cosmetics Regulation 344/2013 (as an amendment to the listing under Annex III of Regulation 1223/2009). 2,2'-[(4-Amino-3-nitrophenyl)imino]bisethanol and its salt may be used as a hair dye substance in ready-for-use preparations of non-oxidising hair dye products at a maximum concentration of 2.5 % (as hydrochloride salt). Additionally, after mixing under oxidative conditions (i.e. with hydrogen peroxide), the maximum concentration applied to hair must not exceed 1.25 % (as hydrochloride salt). The Cosmetics Regulation also mandates label warning statements relating to the sensitisation potential of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol.

2,2'-[(4-Amino-3-nitrophenyl)imino]bisethanol and its salt are also listed, with the same use restrictions as described above for the EU, as follows:

- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III—Part 1.
- The New Zealand Cosmetic Products Group Standard—Schedule 5.

Substance summary

Table 1.5A: Chemical information

Property	2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol	2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol monohydrochloride
CAS No.	29705-39-3	94158-13-1
Alternative names	Ethanol, 2,2'-[(4-amino-3-nitrophenyl)imino]bis- (CAS)	2,2'-((4-amino-3-nitrophenyl)imino)bisethanol hydrochloride; Ethanol, 2,2'-[(4-amino-3-nitrophenyl)imino]bis-, monohydrochloride (CAS); HC Red 13 (INCI)
Chemical structure		
Molecular formula	$C_{10}H_{15}N_3O_4$	$C_{10}H_{16}ClN_3O_4$
Molecular weight	241.2 g/mol	277.7 g/mol

The following information was extracted from the NICNAS IMAP Human Health Tier II group assessment report for Ethanol, 2,2'-[(4-amino-3-nitrophenyl)imino]bis- and its monohydrochloride.[8]

[8] Publicly available from the NICNAS website at: https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=1796

The hazards of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol and its monohydrochloride were assessed together using the toxicological data available. Where data was unavailable for the parent base, the data available for the salt is considered relevant for the hazard assessment due to the structural similarity of the two chemicals. However, the monohydrochloride salt could have different properties from the parent base with respect to local effects.

Table 1.5B: Acute toxicity end-points for 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol hydrochloride

Toxicity	Species	2,2'-((4-amino-3-nitrophenyl)imino)bisethanol hydrochloride	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	2120	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	-
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	N/A	No data	-
Skin irritation	Rabbit	Limited reliability. Not irritating at low concentrations	-
Eye irritation	Rabbit	Limited reliability. Not irritating at low concentrations	-
Skin sensitisation (Local lymph node assay, LLNA)	Mice	Moderate sensitiser	Schedule 6

Acute toxicity

2,2'-((4-Amino-3-nitrophenyl)imino)bisethanol hydrochloride is expected to have low acute toxicity based on results from animal tests following oral exposure. No acute dermal or inhalation toxicity data are available.

Irritation

The limited available data from experimental animal studies, suggest that 2,2'-((4-amino-3-nitrophenyl)imino)bisethanol hydrochloride, at 2.5%, is not irritating to the skin or eyes. However, it is noted that a concentration of 2.5% is too low for hazard evaluation.

Sensitisation

Based on the available data, the chemicals are considered to be moderate skin sensitisers.

- In a LLNA, the monohydrochloride salt, in a mixture of water/acetone (1:1) with olive oil (3:1) or in dimethyl sulfoxide (DMSO), was applied to the surface of the ear of female CBA/J mice (n=5/group) once daily for three consecutive days. The salt at test concentrations of 0.5, 1.5, 5 or 10% in water/acetone/olive oil produced stimulation indices (SIs) of 1.3, 2.2, 1.2 or 1.4, respectively. The estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) could not be calculated as all values were below three. The salt, at test concentrations of 0.5, 1.5, 5 or 10% in DMSO, produced SIs of 1.5, 1.8, 2.1 or 3.5, respectively. The EC3 was 8.2%, indicating a moderate skin sensitisation potential.
- No dermal allergic reaction was reported in a guinea pig maximisation test (GPMT) and a Landsteiner-Draize guinea pig sensitisation test in female Pirbright guinea pigs. However, due to the low test concentrations (1-3%) used in these studies, they were considered inadequate for hazard evaluation.

Repeat-dose toxicity

The available data suggest that the chemicals have low to moderate repeated dose toxicity based on results from animal tests following repeated oral exposure. Based on the limited data available from animal studies, the chemicals are not expected to have systemic toxicity following repeated dermal exposure. No repeated inhalation toxicity data are available.

Genotoxicity

Based on the weight of evidence from the available *in vitro* and *in vivo* genotoxicity studies, the chemicals are not considered to be genotoxic. Positive results were seen in some *in vitro* genotoxicity tests, but all *in vivo* tests were negative.

Carcinogenicity

No carcinogenicity studies are available for the chemicals, except for a dermal study conducted using the salt at low concentrations. The data available do not provide sufficient information to make a conclusion on the carcinogenicity of the chemicals. Based on the available genotoxicity data, the chemicals are not considered to be genotoxic carcinogenic.

Reproduction and developmental toxicity

Based on the available data, the chemicals are not expected to have reproductive or developmental toxicity.

Pre-meeting public submissions

One (1) pre-meeting submission was received in support. The main points were that the new schedule entry would be in alignment with international regulators in the EU, ASEAN and NZ.

Summary of ACCS advice to the delegate

The committee advised that 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol be entered in Schedule 6 under the INCI name, HC Red 13[9] with exemption cut-off concentrations as follows:

Schedule 6 – New Entry

HC RED 13 (including its salts) **except**:

a) in non-oxidative hair dye preparations containing 2.5 per cent or less of HC Red 13 when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and

Written in letters not less than 1.5 mm in height; or

b) in oxidative hair dye preparations containing 1.25 per cent or less of HC Red 13 after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

[9] A public submission received in response to the interim decision indicated that HC Red 13 is the INCI name for the hydrochloride salt of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol specifically. The phrase 'including its salts' in the schedule entry is therefore redundant.

Written in letters not less than 1.5 mm in height.

The committee also that advised that appendix and index entries are created as follow:

Appendix E, Part 2 – New Entry

HC RED 13

Standard statements: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

HC RED 13

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

Index – New Entry

HC RED 13
cross reference: 2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL

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

The committee recommended an implementation date of **1 June 2017**.

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

The reasons for the advice comprised the following:

- HC Red 13 is used cosmetically as a hair dye.
- HC Red 13 is a moderate skin sensitiser consistent with Schedule 6 factors.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is to create a new Schedule 6 entry for 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol under the INCI name, HC Red 13[10] with exemption cut-off concentrations for oxidative and non-oxidative hair dye preparations.

[10] A public submission received in response to the interim decision indicated that HC Red 13 is the INCI name for the hydrochloride salt of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol specifically. The phrase 'including its salts' in the schedule entry is therefore redundant.

The proposed wording for the schedule, appendix and index entries are as follows:

Schedule 6 – New Entry

HC RED 13 (including its salts) **except**:

a) in non-oxidative hair dye preparations containing 2.5 per cent or less of HC Red 13 when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and

Written in letters not less than 1.5 mm in height; or

b) in oxidative hair dye preparations containing 1.25 per cent or less of HC Red 13 after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

HC RED 13

Standard statements: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

HC RED 13

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

Index – New Entry

HC RED 13
cross reference: 2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL

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

The proposed implementation date is **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (b) the purposes for which a substance is to be used and the extent of use of a substance; and (c) the toxicity of a substance.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- 2,2'-[(4-Amino-3-nitrophenyl)imino]bisethanol and its monohydrochloride (HC Red 13) are used cosmetically in hair dyes.

- 2,2'-[(4-Amino-3-nitrophenyl)imino]bisethanol and its monohydrochloride (HC Red 13) are moderate skin sensitisers consistent with Schedule 6 factors.

Public submissions on the interim decision

One (1) submission was received which supported the delegate's interim decision with amendments. The main point in support was that the proposed schedule entry concentration cut-offs would be in alignment with international regulations in the EU. The main points were:

- Incorrect use of synonyms. HC Red 13 is the INCI name for the hydrochloride salt of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol. The phrase '*including its salts'* in the schedule entry is therefore redundant.
- No Appendix E Standard Statements are proposed. The submission suggests that Standard Statements should be applied in a way that is consistent with other existing entries for scheduled hair dye substances.
- The submission questions the use of the warning statement, '*This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye'* and whether the reason for its inclusion is eye irritancy or sensitisation.
- The appropriateness of the proposed 'earliest possible implementation date' of 1 June 2017. The submission stresses that an adequate transition period of at least 12 months must be allowed for any labelling changes and/or reformulation that may be required where no immediate risk has been identified; and that there is no evidence to suggest immediate action is required for the risk management of this substance.

Delegate's final decision

The delegate's final decision is to create a new Schedule 6 entry for 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol with exemption cut-off concentrations for oxidative and non-oxidative hair dye preparations and new Appendices E & F and Index entries as follows:

Schedule 6 – New Entry

2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL (including its salts) **except**:

a) in non-oxidative hair dye preparations containing 2.5 per cent or less of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol after mixing when the immediate container and primary pack are labelled with the following statements:

> KEEP OUT OF REACH OF CHILDREN, and
> WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and
> Written in letters not less than 1.5 mm in height; or

b) in oxidative hair dye preparations containing 1.25 per cent or less of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements:

> KEEP OUT OF REACH OF CHILDREN, and
> WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and
> Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL

Standard statements: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

Index – New Entry

2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL
cross reference: HC RED 13

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

HC RED 13
cross reference: 2,2'-[(4-AMINO-3-NITROPHENYL)IMINO]BISETHANOL

The implementation date has been extended to **1 February 2018.**

The delegate confirms that the reasons for the final decision are the same as those provided from the interim decision. Additional reasons for the final decision include:

- The delegate notes that HC Red 13 specifically refers to the hydrochloride salt of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol and has amended the wording of the schedule entry to capture all salts of 2,2'-[(4-amino-3-nitrophenyl)imino]bisethanol.
- The words *'after mixing*' have been added to the schedule entry for clarity
- The delegate notes that a longer implementation time is required to allow for labelling changes and/or reformulation.

1.6 HC Violet 1 (2-[(4-amino-2-methyl-5-nitrophenyl)amino]-ethanol)

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new Schedule 6 entry for 2-[(4-amino-2-methyl-5-nitrophenyl)amino]-ethanol in hair dyes and eyebrow/eyelash colouring products and to determine whether an appropriate exemption cut-off is required.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 6 – New Entry

2-[(4-AMINO-2-METHYL-5-NITROPHENYL)AMINO]ETHANOL **except** when used in hair dye preparations containing 0.25 per cent or less of 2-[(4-amino-2-methyl-5-nitrophenyl)amino]ethanol under oxidative conditions (after mixing with hydrogen peroxide), or 0.28 per cent or less of 2-[(4-amino-2-methyl-5-nitrophenyl)amino]ethanol under non-oxidative conditions, and when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN; and

WARNING – This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5mm in height

Appendix E, Part 2 – New Entry

2-[(4-AMINO-2-METHYL-5-NITROPHENYL)AMINO]ETHANOL

Standard statements: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

2-[(4-AMINO-2-METHYL-5-NITROPHENYL)AMINO]ETHANOL

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

The applicant's reasons for the request are:

- 2-[(4-Amino-2-methyl-5-nitrophenyl)amino]-ethanol (HC Violet 1) has reported cosmetic use in semi-permanent hair dye preparations in Australia.
- HC Violet 1is a strong skin sensitiser.
- The overseas restrictions for HC Violet 1 in hair dyes state that the maximum concentration allowed in the finished cosmetic product in hair dye products is 0.28% and the maximum use concentration upon application is 0.25% (after mixing under oxidative conditions).
- The risk could be controlled by including warning statements on the label of hair dye formulations containing HC Violet 1 at any concentration.
- As a strong sensitiser, HC Violet 1 presents a serious risk of sensitisation even below the maximum concentration of 0.28% permitted under the EU Cosmetic Regulation. Given the potential for induction and elicitation of sensitisation below the EU cut-off, the risk would be better controlled by inclusion of appropriate cut-offs and warning statements on the label of preparations containing the chemical below the cut-off. This is consistent with Schedule 6 entries for some other hair dye ingredients.

Current scheduling status and relevant scheduling history

2-[(4-Amino-2-methyl-5-nitrophenyl) amino]-ethanol (HC Violet 1) is not currently scheduled and has not been previously considered for scheduling; therefore, a scheduling history is not available.

Australian regulatory information

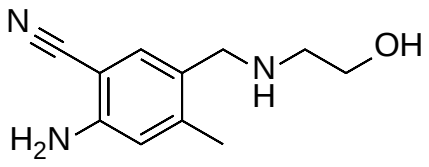
2-[(4-Amino-2-methyl-5-nitrophenyl) amino]-ethanol is reported to be used in semi-permanent hair dye preparations in Australia (NICNAS, 2007). Currently, there are no restrictions in Australia on using this chemical in cosmetic products. In the absence of any regulatory controls, the characterised critical health effects (skin sensitisation) have the potential to pose an unreasonable risk to public under the uses identified.

International regulations

The European Union (EU), New Zealand and the Association of South East Asian Nations (ASEAN) have restricted the use of the chemical in cosmetics: '(a) the maximum authorised concentration in the finished cosmetic products as hair dye substances in non-oxidative hair dye products is 0.28 %; and (b) after mixing with hydrogen peroxide under oxidative conditions the maximum concentration applied to hair must not exceed 0.25 %'. The EU Cosmetics Regulation No. 344/2013 Annex III, Part 1 also mandates label warning statements relating to the sensitisation potential of the chemical at lower concentrations.

Substance summary

Table 1.6A: Chemical information

Property	2-[(4-amino-2-methyl-5-nitrophenyl)amino]-ethanol
CAS No.	82576-75-8
Alternative names	HC Violet 1(INCI); Imexine FAA; 1-amino-3-methyl-4-(2-hydroxyethyl)amino-6-nitrobenzene; ethanol, 2-[(4-amino-2-methyl-5-nitrophenyl)amino]- (CAS)
Chemical structure	
Molecular formula	$C_9H_{13}N_3O_3$
Molecular weight	211.2 g/mol

The following information was extracted from the NICNAS IMAP Human Health Tier II assessment report for Ethanol, 2-[(4-amino-2-methyl-5-nitrophenyl)amino]-.[11]

Table 1.6B: Acute toxicity end-points for 2-[(4-amino-2-methyl-5-nitrophenyl) amino]-ethanol (HC Violet 1)

Toxicity	Species	HC Violet 1	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2000	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	N/A	No data	N/A
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	N/A	No data	N/A
Skin irritation	Rabbit	Slight irritant	N/A
Eye irritation	Rabbit	Slight irritant	N/A
Skin sensitisation (local lymph node assay, LLNA)	Mouse	Strong sensitiser	Schedule 6

Sensitisation

Based on the available data, the chemical is considered to be a strong skin sensitiser:

- One LLNA (OECD TG 429) was conducted in female CBA/J mice (n = 5/concentration), using 2-[(4-amino-2-methyl-5-nitrophenyl) amino]-ethanol in dimethyl formamide (DMF) vehicle. All test concentrations of 1, 2.5, 5, 10 and 25% produced a stimulation index (SI) over three (4.08, 6.11, 9.11, 5.64 and 9.79, respectively). The effective concentration needed to produce a three-fold

[11] Publicly available on the NICNAS website at: https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1795#cas-A_82576-75-8

increase in lymphocyte proliferation (EC3), which was calculated to less than 1%, indicated a strong sensitising potential.

- In another LLNA (OECD TG 429), in female CBA/J mice (n = 5/concentration), using 2-[(4-amino-2-methyl-5-nitrophenyl) amino]-ethanol in DMF vehicle also, test concentrations of 0.1, 0.25, 0.5, 1 and 2.5% produced an SI of 1.20, 1.67, 1.30, 3.40, 3.83 and 11.05, respectively. The EC3 value, which was calculated to be 0.9%, indicated a strong sensitising potential.

Repeat-dose toxicity

Based on the available data, 2-[(4-amino-2-methyl-5-nitrophenyl) amino]-ethanol is not expected to cause serious damage to health from repeated oral exposure. No information was available for repeated dose toxicity by dermal and inhalation routes.

Genotoxicity

Based on the negative results observed in several in vitro and in vivo genotoxicity studies, 2-[(4-amino-2-methyl-5-nitrophenyl) amino]-ethanol is not expected to be genotoxic.

Carcinogenicity

No data are available for carcinogenicity. However, the lack of genotoxicity in vivo and negative bacterial reverse mutation assay results indicates that the likelihood of carcinogenic effects is low.

Reproduction and developmental toxicity

Based on the limited available data, 2-[(4-amino-2-methyl-5-nitrophenyl) amino]-ethanol is not expected to have reproductive and developmental toxicity.

Pre-meeting public submissions

One (1) pre-meeting submission was received in support. The main points were that the new schedule entry would be in alignment with international regulators in the EU, ASEAN and NZ.

Summary of ACCS advice to the delegate

The committee advised that a new Schedule 6 entry for 2-[(4-amino-2-methyl-5-nitrophenyl)amino]-ethanol be created under the INCI name of HC Violet 1 with exemption cut-off concentrations as follows:

Schedule 6 – New Entry

HC VIOLET 1 **except**:

a) in non-oxidative hair dye preparations containing 0.28 per cent or less of HC Violet 1 when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and

Written in letters not less than 1.5 mm in height; or

b) in oxidative hair dye preparations containing 0.25 per cent or less of HC Violet 1 after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions

should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

Written in letters not less than 1.5 mm in height.

The committee also advised that appendix and index entries be created as follows:

Appendix E, Part 2 – New Entry

HC VIOLET 1

Standard statements: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

HC VIOLET 1

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

Index – New Entry

HC VIOLET 1
cross reference: 2-[(4-AMINO-2-METHYL-5-NITROPHENYL)AMINO]-ETHANOL

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

The committee recommended an implementation date of **1 June 2017**.

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

The reasons for the advice comprised the following:

- HC Violet 1 is used in hair dyes, and dermal contact is unavoidable.
- HC Violet 1 has demonstrated strong skin sensitisation potential consistent with Schedule 6 factors.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is to create a new Schedule 6 entry for 2-[(4-amino-2-methyl-5-nitrophenyl)amino]-ethanol under the INCI name of HC Violet 1 with exemption cut-off concentrations.

The proposed wording for the schedule, appendix and index entries are as follows:

Schedule 6 – New Entry

HC VIOLET 1 **except**:

a) in non-oxidative hair dye preparations containing 0.28 per cent or less of HC Violet 1 when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and

Written in letters not less than 1.5 mm in height; or

b) in oxidative hair dye preparations containing 0.25 per cent or less of HC Violet 1 after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and

Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

HC VIOLET 1

Standard statements: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

HC VIOLET 1

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

Index – New Entry

HC VIOLET 1
cross reference: 2-[(4-AMINO-2-METHYL-5-NITROPHENYL)AMINO]-ETHANOL

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

The proposed implementation date is **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (b) the purposes for which a substance is to be used and the extent of use of a substance; and (c) the toxicity of a substance.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- HC Violet 1 is used in hair dyes, and dermal contact is unavoidable.

- HC Violet 1 has demonstrated strong skin sensitisation potential consistent with Schedule 6 factors.

Public submissions on the interim decision

One (1) submission was received which supported the delegate's interim decision with amendments. The main point in support was that the proposed schedule entry concentration cut-offs would be in alignment with international regulations in the EU. The main points were:

- No Appendix E Standard Statements are proposed. The submission suggests that Standard Statements should be applied in a way that is consistent with other existing entries for scheduled hair dye substances.
- The submission questions the use of the warning statement, '*This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye'* and whether the reason for its inclusion is eye irritancy or sensitisation.
- The appropriateness of the proposed 'earliest possible implementation date' of 1 June 2017. The submission stresses that an adequate transition period of at least 12 months must be allowed for any labelling changes and/or reformulation that may be required where no immediate risk has been identified; and that there is no evidence to suggest immediate action is required for the risk management of this substance.

Delegate's final decision

The delegate's final decision is to create a new Schedule 6 entry for 2-[(4-amino-2-methyl-5-nitrophenyl)amino]-ethanol under the INCI name of HC Violet 1 with exemption cut-off concentrations; and to create new Appendices E & F and Index entries as follows:

Schedule 6 – New Entry

HC VIOLET 1 (2-[(4-amino-2-methyl-5-nitrophenyl)amino]-ethanol **except**:

a) in non-oxidative hair dye preparations containing 0.28 per cent or less of HC Violet 1 after mixing when the immediate container and primary pack are labelled with the following statements:

> KEEP OUT OF REACH OF CHILDREN, and
> WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use, and
> Written in letters not less than 1.5 mm in height; or

b) in oxidative hair dye preparations containing 0.25 per cent or less of HC Violet 1 after mixing under oxidative conditions when the immediate container and primary pack are labelled with the following statements:

> KEEP OUT OF REACH OF CHILDREN, and
> WARNING - This product contains ingredients which may cause skin sensitisation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye, and
> Written in letters not less than 1.5 mm in height.

Appendix E, Part 2 – New Entry

HC VIOLET 1

Standard statements: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

HC VIOLET 1

Warning statements: 28 ((over) (repeated) exposure may cause sensitisation).

Index – New Entry

HC VIOLET 1
cross reference: 2-[(4-AMINO-2-METHYL-5-NITROPHENYL)AMINO]-ETHANOL

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

The implementation date has been extended to **1 February 2018.**

The delegate confirms that the reasons for the final decision are the same as those provided from the interim decision. Additional reasons for the final decision include:

- The warning statement 'This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye' has been included to caution the use of HC Violet 1 when used under oxidative conditions (when mixed with hydrogen peroxide).
- The words *'after mixing'* have been added to the schedule entry for clarity
- The delegate notes that a longer implementation time is required to allow for labelling changes and/or reformulation.

1.7 Abamectin

Referred scheduling proposal

An application was submitted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) to amend the Schedule 5 entry for abamectin to accommodate preparations containing 0.05 per cent or less of abamectin in a gel formulation.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 5 – Amend Entry

ABAMECTIN:

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

b) in preparations containing 0.05 per cent or less of abamectin formulated as ready to use cockroach bait gel in application syringes containing no more than 100 g of product.

The applicant's reasons for the request are:

- The product, PestXpert DIY Pest Control Like The Professionals Cockroach Bait, contains 0.5 g/kg (0.05%) abamectin in a preparation for pesticidal use that is not for internal use for the treatment of animals and would therefore be considered a Schedule 6 poison. Sumitomo Chemical Australia Pty Ltd is seeking a new entry in Schedule 5 for preparations containing 0.05% of abamectin, or less.
- The other active constituent in the product, pyriproxyfen, is included in Appendix B of the Poisons Standard, based on its low toxicity profile, when used as a pesticide.

- Based on acute toxicity studies using a surrogate formulation with the same abamectin content (0.05%), the product is considered to have low acute oral toxicity (LD50 >5000 mg/kg bw) and low acute dermal toxicity (LD50 >5000 mg/kg bw). The product was a slight eye irritant but not a skin irritant.
- Given the proposed product formulation, packaging and recommended use pattern, oral exposure is not expected. Nonetheless, if accidental ingestion by a child (20 kg bw) of the product containing 0.05% abamectin from a ready to use syringe was to occur, it would be well under the ARfD for abamectin.
- Minimal exposure is expected from the application of the ready to use gel formulation available in 10-100 g sealed syringes. Bystander exposure is considered unlikely.
- The effect of skin sensitisation by the product can be adequately managed through the labelling statements which recommend that applicators wear gloves.

Current scheduling status

Abamectin is currently listed in Schedules 7, 6 and 5 and is also included in Appendix J, Part 2 as follows:

Schedule 7

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

Schedule 6

ABAMECTIN:

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

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

Schedule 5

ABAMECTIN in preparations, for internal use for the treatment of animals, containing 1 per cent or less of abamectin.

Appendix J, Part 2 – ABAMECTIN

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

Relevant scheduling history

Abamectin has been considered several times by the committee, both on its own, and in combination with other substances.

Abamectin was first considered in November 1984 as avermectin. In November 1984, the Poisons Schedule (Standing) Committee (PSC) considered scheduling of a 1 per cent avermectin B1 (a synonym for abamectin) injection to be used as an antiparasitic agent in animals. Based on toxicity, PSC decided to include this substance in Schedule 7. However, the PSC also noted the intent to only market a sealed container product for use with automated injection equipment and agreed to a Schedule 6 cut-off for such preparations when included in 10 mL or less injections.

In May 1992, the Drugs and Poisons Schedule Standing Committee (NDPSC) agreed to a request to change the name of avermectin B1 in the schedule entries to abamectin, noting that this was the name approved by the Standards Association of Australia (now called Standards Australia).

In August 1994, the NDPSC decided to include emulsifiable concentrate formulations containing abamectin at 18 g/L or less in Schedule 6.

In August 1995, NDPSC agreed to include ≤ 1 per cent abamectin for animal internal use in Schedule 5.

In June 2008, the NDPSC decided also to include slow-release plastic matrix ear tags for livestock use containing 1 g or less of abamectin in Schedule 6.

In October 2009, the NDPSC considered whether preparations for pesticidal use containing 0.0015 per cent or less of abamectin were consistent with the Schedule 5 criteria. It was agreed that although low concentration of abamectin were likely to be less hazardous, because insufficient data had been provided to allay the concern regarding the high acute oral, dermal and inhalation toxicity of abamectin, it was decided that the existing scheduling was appropriate.

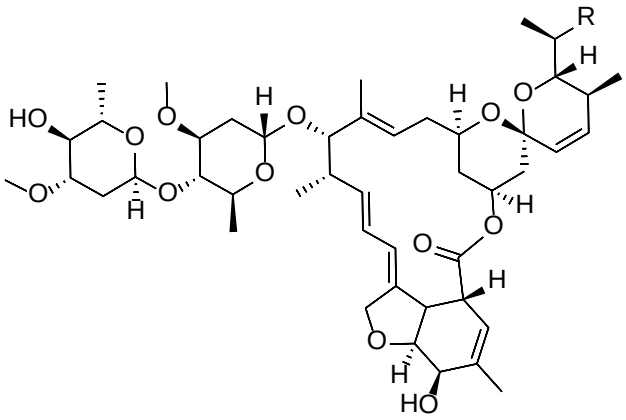
Following recommendation of the March 2013 Advisory Committee on Chemicals Scheduling (ACCS), Schedule 6 cut-off for abamectin in preparations for pesticidal use has been increased from 2 per cent to 4 per cent or less of abamectin, except when included in Schedule 5, or in slow-release plastic matrix ear tags for livestock use containing 1 g or less of abamectin.

Australian regulatory information

As an AgVet chemical, abamectin is subject to labelling requirements according to the First Aid Instruction and Safety Directions (FAISD) Handbook.

Substance summary

Table 1.7A: Chemical information

Property	Abamectin
CAS No.	Abamectin: 71751-41-2 containing 65195-55-3 (abamectin B_{1a}) and 65195-56-4 (abamectin B_{1b}).
Chemical structure	 Abamectin B_{1a} R = CH_2CH_3 Abamectin B_{1b} R = CH_3

Property	Abamectin
Alternative names	Abamectin: mixture of ≥80% abamectin B_{1a} & <20% abamectin B_{1b} Abamectin B_{1a}: (10E,14E,16E)-(1R,4S,5′S,6S,6′R,8R,12S,13S,20R,21R,24S)-6′-[(S)-sec-butyl]-21,24-dihydroxy-5′,11,13,22-tetramethyl-2-oxo-(3,7,19-trioxatetracyclo[15.6.1.14,8.020,24]pentacosa-10,14,16,22-tetraene)-6-spiro-2′-(5′,6′-dihydro-2′H-pyran)-12-yl 2,6-dideoxy-4-O-(2,6-dideoxy-3-O-methyl-α-L-arabino-hexopyranosyl)-3-O-methyl-α-L-arabino-hexopyranoside Abamectin B_{1b}: (10E,14E,16E)-(1R,4S,5′S,6S,6′R,8R,12S,13S,20R,21R,24S)-21,22-dihydroxy-6′-isopropyl-5′,11,13,22-tetramethyl-2-oxo-(3,7,19-trioxatetracyclo[15.6.1.14,8.020,24]pentacosa-10,14,16,22-tetraene)-6-spiro-2′-(5′,6′-dihydro-2′H-pyran)-12-yl 2,6-dideoxy-4-O-(2,6-dideoxy-3-O-methyl-α-L-arabino-hexopyranosyl)-3-O-methyl-α-L-arabino-hexopyranoside.

The following toxicology information was extracted from the Office of Chemical Safety (OCS) human health risk assessment technical report for Abamectin, Pyriproxyfen (product name PestXPert DIY Pest Control Like the Professionals Cockroach Bait).

Table 1.7B: Acute toxicity end-points for a formulated product that was considered by the OCS to be an acceptable surrogate to the proposed product containing 0.05% abamectin and 0.5% pyriproxyfen

Toxicity	Species	Product containing abamectin (0.05%)	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>5000	N/A
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>5000	N/A
Acute inhalational toxicity LC_{50} ($mg/m^3/4h$)	No data	No data	N/A
Skin irritation	Rabbit	Non-irritant	N/A
Eye irritation	Rabbit	Slight irritant	Schedule 5
Skin sensitisation (Buehler Method)	Guinea pigs	Sensitiser	–

Pre-meeting public submissions

No pre-meeting submissions were received for abamectin.

Summary of ACCS advice to the delegate

The committee advised that Schedule 5 entry for abamectin in the Poisons Standard be amended to include gel formulations containing 0.05 per cent or less of abamectin as follows:

Schedule 5 – Amend Entry

ABAMECTIN:

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

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

The committee also recommended an implementation date of **1 June 2017**.

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

The reasons for the advice comprised the following:

- Abamectin is a skin sensitiser.
- Abamectin at this concentration and in this dose form has an inferred toxicity profile consistent with Schedule 5 factors, based on a surrogate formulation.
- Products containing abamectin at this concentration and in this dose form should labelled to ensure the use of appropriate personal protective equipment.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is to amend the Schedule 5 entry for abamectin to include gel formulations containing 0.05 per cent or less of abamectin.

The proposed wording for the schedule entry is as follows:

Schedule 5 – Amend Entry

ABAMECTIN:

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

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

The proposed implementation date is **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (a) the risks and benefits of the 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 interim decision are the following:

- The delegate acknowledges the committee's advice.

- Abamectin is a skin sensitiser.
- Abamectin at this concentration and in this dose form has an inferred toxicity profile consistent with Schedule 5 factors, based on a surrogate formulation.
- Products containing abamectin at this concentration and in this dose form should labelled to ensure the use of appropriate personal protective equipment.

Public submissions on the interim decision

No submissions were received for abamectin.

Delegate's final decision

The delegate has confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegate's final decision is to amend the Schedule 5 entry for abamectin to include gel formulations containing 0.05 per cent or less of abamectin. The implementation date is **1 June 2017**.

1.8 1-Deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create a new Schedule 6 entry for 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives; to consider if an exemption cut-off for rinse-off cosmetics and household cleaning products is appropriate; and to determine whether an Appendix E listing for 1-deoxy-1-(methylamino)-D-Glucitol *N*-coco acyl derivatives is required.

Scheduling application

This is a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 6 – New Entry

1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL *N*-COCO ACYL DERIVATIVES in cosmetic and household cleaning preparations **except**:

a) in wash-off preparations containing 5 per cent or more of 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives, labelled with warning to the follow effect:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER; and

b) in preparations containing 30 per cent or more of 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives.

Appendix E, Part 2 – New Entry

1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL *N*-COCO ACYL DERIVATIVES

Standard statement: E1 (if in eyes wash out immediately with water).

The applicant's reasons for the request are:

- 1-Deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives is a severe irritant as tested in vivo with a GHS hazard classification of Category 1 serious eye damage/eye irritation and a hazard statement of H318 – causes serious eye damage;
- The substance is used as a surfactant in rinse-off cosmetics at a concentration ≤8% and household cleaning products at a concentration ≤10%. Widespread and repeated public exposure is expected. The finished products include cleansing products for skin/hair, laundry, dishwashing and hard surface cleaning;

- The NICNAS assessment indicates that the hazard and risk characteristics of the substance conform to Scheduling Policy Framework factors for Schedule 6, specifically severe eye irritation (corneal opacity not reversible in 21 days concurrent with conjunctiva redness, chemosis and discharge);
- Irreversible eye damage or severe eye irritation effects can occur when consumers use the products containing relatively high concentrations of the substance especially hair/skin cleansing products and come into direct contact with the products in eyes; and
- Reasonable foreseeable harm to users can be reduced through strong label warnings and extensive safety directions. Setting a concentration cut-off for the substance can protect consumers from serious eye damage. Wash-off preparations containing more than 5% of the substance should be labelled and preparations containing more than 30% of the substance should be included in Schedule 6 even when they are labelled.

Current scheduling status and relevant scheduling history

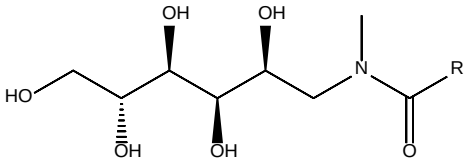
1-Deoxy-1-(methylamino)-D-Glucitol *N*-coco acyl derivatives are not currently scheduled and have not been previously considered for scheduling; therefore, a scheduling history is not available.

Australian regulatory information

The public exposure to the substance is widespread and repeated. The principal route of exposure is dermal, while ocular exposure is highly possible. Based on current use proposals, the exposure to the substance is up to 8% concentration in rinse-off cosmetics for skin and hair cleansing and at up to 10% concentration in household cleaning products. Without warnings and appropriate directions, use of above consumer products could result in severe eye irritations to users. Setting a concentration cut-off for the substance used in cosmetics and household products, and providing users with labelling and first aid information could protect consumers.

Substance summary

Table 1.8A: Substance summary

Property	1-Deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives
CAS No.	1591783-13-9
Alternative names	Cocoyl Methyl Glucamaide (INCI Name); D-Glucitol, 1-deoxy-1-(methylamino)-, *N*-coco acyl derivatives (CAS)
Chemical structure	 Where R = C7-C17 alkyl group or C17 alkenyl group

The following toxicology information was extracted from the NICNAS New Chemical assessment report for D-Glucitol, 1-deoxy-1-(methylamino)-, *N*-coco acyl derivs.[12]

[12] Publicly available on the NICNAS website.

Table 1.8B: Acute toxicity endpoints for 1-deoxy-1-(methylamino)-D-Glucitol *N*-coco acyl derivatives

Toxicity	Species	1-Deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rat	>2,000	Schedule 5
Acute dermal toxicity LD_{50} (mg/kg bw)	Rat	>2,000	None
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Not provided	Not provided	N/A
Skin irritation	*In vitro*	Non-irritating	None
Eye irritation	Rabbit	Severely irritating	Schedule 6
Skin sensitisation (LLNA / Buehler etc)	Guinea pig	No evidence of sensitisation	None

Acute toxicity

Based on studies provided, 1-deoxy-1-(methylamino)-D-Glucitol N-coco acyl derivatives are of low acute oral and dermal toxicity. However, 1 of 3 test animals died of the treatment at 2000 mg/kg bw in the acute oral toxicity study.

Irritation

An *in vitro* study on eye irritation using bovine corneal opacity and permeability test method indicated that the substance may have potential for eye irritation. Subsequent eye irritation study in rabbits demonstrated that 1-deoxy-1-(methylamino)-D-Glucitol N-coco acyl derivatives are severely irritating to the eyes. A single ocular application of the substance produced severe irritation effects. These effects included corneal opacity, conjunctiva redness, chemosis and discharge that were not reversible within 21 days after the application in 2 of 3 test animals. The results warranted following classification of the substance under GHS:

Hazard classification	**Hazard statement**
Serious eye damage/eye irritation (Category 1)	H318 – Causes serious eye damage

Sensitization

Guinea pig maximisation test on the substance at up to 5% concentration did not reveal evidence of skin sensitisation.

Repeat-dose toxicity

In a 28 day repeated dose oral toxicity study on 1-deoxy-1-(methylamino)-D-Glucitol N-coco acyl derivatives, no treatment-related adverse effects were observed in the test animals at any dose tested.

Mutagenicity

1-Deoxy-1-(methylamino)-D-Glucitol N-coco acyl derivatives tested negative in bacterial reverse mutation assay and *in vitro* mammalian cell gene mutation tests.

Genotoxicity

1-Deoxy-1-(methylamino)-D-Glucitol N-coco acyl derivatives tested negative in an *in vivo* mouse bone marrow micronucleus test via the oral route.

Public exposure

1-Deoxy-1-(methylamino)-D-Glucitol N-coco acyl derivatives are used as a surfactant-cleaning agent in consumer products with widespread and repeated public exposure. The finished products include cleansing products for skin/hair, laundry, dishwashing and hard surface cleaning.

Pre-meeting public submissions

One (1) pre-meeting submission was received which opposed the scheduling proposal. The main points are in relation to the toxicity and risks of 1-deoxy-1-(methylamino)-D-glucitol *N*-coco-acyl derivatives; and the scheduling inconsistencies and international regulations of similar surfactants.

Summary of ACCS advice to the delegate

The committee advised that a new Schedule 6 entry be created for 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives with exemptions and cut-offs as follows:

Schedule 6 – New Entry

1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL *N*-COCO ACYL DERIVATIVES **except:**

a) in cosmetic rinse-off preparations containing 8 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives when labelled the following statement:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER, or

b) in household cleaning preparations, other than those intended to be sprayed, containing 10 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives when labelled with the following statement:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER.

The committee also advised appendix and index entries as follows:

Appendix E, Part 2 – New Entry

1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL *N*-COCO ACYL DERIVATIVES

Standard statement: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL *N*-COCO ACYL DERIVATIVES

Warning statement: 79 (Will irritate eyes).
Safety direction: 1 (Avoid contact with eyes)

Index – New Entry

1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL *N*-COCO ACYL DERIVATIVES
cross reference: cocoyl methyl glucamaide

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

The committee recommended an implementation date of 1 **June 2017**.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (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 comprised the following:

- 1-Deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives is used as a surfactant.
- 1-Deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives is a severe eye irritant, which can be managed by labelling at low concentrations in rinse-off products.
- The risk of spray products containing 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives entering the eye is high.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is to create a new Schedule 6 entry for 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives with exemptions and cut-offs in cosmetic rinse-off preparations and household cleaning preparations.

The proposed wording for the schedule, appendix and index entries is as follows:

Schedule 6 – New Entry

1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL *N*-COCO ACYL DERIVATIVES **except:**

a) in cosmetic rinse-off preparations containing 8 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives when labelled the following statement:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER, or

b) in household cleaning preparations, other than those intended to be sprayed, containing 10 per cent or less of 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives when labelled with the following statement:

IF IN EYES WASH OUT IMMEDIATELY WITH WATER.

Appendix E, Part 2 – New Entry

1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL *N*-COCO ACYL DERIVATIVES

Standard statement: E1 (if in eyes wash out immediately with water).

Appendix F, Part 3 – New Entry

1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL *N*-COCO ACYL DERIVATIVES

Warning statement: 79 (Will irritate eyes).
Safety direction: 1 (Avoid contact with eyes)

Index – New Entry

1-DEOXY-1-(METHYLAMINO)-D-GLUCITOL *N*-COCO ACYL DERIVATIVES
cross reference: cocoyl methyl glucamaide

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

The proposed implementation date is **1 June 2017.**

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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 interim decision are the following:

- The delegate acknowledges the committee's advice.
- 1-Deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives is used as a surfactant.
- 1-Deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives is a severe eye irritant, which can be managed by labelling at low concentrations in rinse-off products.
- The risk of spray products containing 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives entering the eye is high.

Public submissions on the interim decision

One (1) public submission was received which opposed the interim decision. The main points were:

- the proposed scheduling of 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives is too restrictive based on the limited use pattern identified. Should new uses be identified with lower risk profiles, the scheduling decision may need to be revisited.
- the schedule entry for 1-deoxy-1-(methylamino)-D-glucitol *N*-coco acyl derivatives should more closely resemble that for lauryl sulfate salts.
- The appropriateness of the proposed 'earliest possible implementation date' of 1 June 2017. The submission stresses that an adequate transition period of at least 12 months must be allowed for any labelling changes and/or reformulation that may be required where no immediate risk has been identified; and that there is no evidence to suggest immediate action is required for the risk management of this substance.

Delegate's final decision

The delegate's final decision is to create a new Schedule 6 entry for 1-deoxy-1-(methylamino)-D-glucitol N-coco acyl derivatives with exemptions and cut-offs in cosmetic rinse-off preparations and household cleaning preparations. The implementation date has been extended to **1 February 2018.**

The delegate confirms that the reasons for the final decision are the same as those provided from the interim decision. Additional reasons for the final decision include:

- The delegate notes that a longer implementation time is required to allow for labelling changes and/or reformulation.

1.9 *o*-Toluidine and *o*-anisidine

Referred scheduling proposal

An application was submitted by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to create new Schedule 10 entries for *o*-toluidine and *o*-anisidine for use in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 10 – New Entries

o-TOLUIDINE in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows.

o-ANISIDINE in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows.

The applicant's reasons for the request are:

- As part of activities undertaken by NICNAS in 2014-15, o-toluidine and o-anisidine were identified as impurities in tattoo inks in Australia. The chemicals have been detected in hair dye samples overseas.
- The chemicals are mutagenic and carcinogenic following long-term repeated exposure. A genotoxic mode of action is suggested by the available evidence.
- There is an increasing popularity of body adornment through tattoos or permanent make-up (PMU). Tattoos result in long term exposure to the injected chemicals.
- There are international restrictions on the presence of these amines in cosmetic products and tattoo ink preparations (see references).
- The schedule 10 (Appendix C) entry for 2,4-toluenediamine (an aromatic amine with similar toxicological profile) was recently amended to include use in tattoos.
- The inclusion in Schedule 10 is consistent with other aromatic amines with similar toxicological profiles such as 2,4-toluene diamine and would cover the presence of the chemical as an impurity.

Current scheduling status and relevant scheduling history

Neither *o*-anisidine nor *o*-toluidine are specifically scheduled. The chemicals are named as part of Schedule 7 entry for azo dyes as follows:

Schedule 7

AZO DYES that are derivatives by diazotisation of any of the following substances:

p-aminoazobenzene (CAS No. 60-09-3)

o-aminoazotoluene (CAS No. 97-56-3)

o-anisidine (CAS No. 90-04-0)

p-chloroaniline (CAS No. 106-47-8)

4-chloro-o-toluidine (CAS No. 95-69-2)

6-methoxy-m-toluidine (p-cresidine) (CAS No. 120-71-8)

2-naphthylamine (CAS No. 91-59-8)

5-nitro-o-toluidine (CAS No. 99-55-8)

2,4-toluenediamine (CAS No. 95-80-7)

o-toluidine (CAS No. 95-53-4)

2,4,5-trimethylaniline (CAS No. 137-17-7)

o-Toluidine and *o*-anisidine were first included in Schedule 7 in February 2016 as part of the azo dyes entry due to their carcinogenicity and genotoxicity (see section Current scheduling status above). The toxicological data for both *o*-toluidine and *o*-anisidine were provided by NICNAS to support the application for the scheduling of azo dyes at the August 2015 Advisory Committee for Chemicals Scheduling (ACCS) meeting. The reports provided at the August 2015 meeting were the same as those provided with this application.

o-Toluidine and *o*-anisidine are not otherwise specifically scheduled.

Australian regulatory information

The chemicals have been detected in tattoo inks in Australia. It was not possible to identify all popular tattoo inks used in Australia. Of the 49 tattoo inks analysed:

- 6 tattoo inks contained o-toluidine at concentrations between 20 and 89 ppm.
- 15 tattoo inks contained o-anisidine at concentrations between 15 and 77 ppm.

The limit of detection for the assay was 5 ppm.

The data analysis conducted by NICNAS suggests that for the majority of amine-containing tattoo inks, the amines are introduced at some point during manufacture rather than as a result of the reduction of the azo colourants. The pigments used in tattoos are not produced specifically for such application and purity is on average around 70-90 % (European Commission, 2015; European Commission, 2016).

The popularity of tattoos is reported to have increased in the last decade. Based on a survey completed by a representative sample of 8656 men and women ages 16-64 years in Australia, the prevalence of tattoos was reported to be 14.5 % in men and 13.6 % in women. Tattoo prevalence in young adults may represent more than double (European Commission, 2015).

The chemicals have also been detected in tattoo inks (overseas) (European Commission, 2015, p180). The brands in which the chemicals were detected are reported to be available in Australia. Two thirds of the RAPEX notifications in Europe are reported to pertain to imported products, with the highest percentages from the United States (European Commission, 2015). Therefore it is considered likely that these tattoo inks could be imported into Australia.

The chemicals have also been detected in permanent hair dyes and commercial henna samples (colours not specified) overseas. In the absence of specific Australian data, this is considered to be representative of Australian use.

International regulations

o-Toluidine and *o*-anisidine are restricted under Annex XVII to REACH Regulations. 'The chemical cannot be used in substances and preparations placed on the market for sale to the general public in individual concentrations $\geq$0.1 %' (European Parliament and Council 1999; European Parliament and Council 2006; European Parliament and Council 2008). *o*-Toluidine and *o*-anisidine are also included as part of 22 aromatic amines listed in Appendix 8 which places restrictions on their presence in leather or textile articles.

o-Toluidine and *o*-anisidine are on the candidate list of substances of very high concern (SVHC) for eventual inclusion in Annex XIV (ECHA, 2013). In the EU, companies could have legal obligations if the chemical that they produce, supply or use is included on the candidate list whether on its own, in mixtures, or present in articles.

ResAP (2008)1 specifies requirements for the composition, labelling, uses and risk evaluation of tattoo inks in the European Union. ResAP (2008)1 lists 27 aromatic amines (including o-toluidine and o-anisidine) that should not be present in tattoo inks or released from azo-colourants in concentrations that are technically avoidable. The non-binding ResAP are the reference for the national legislation in several European countries and New Zealand (NZ EPA, 2012).

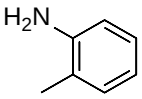
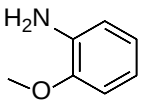
o-Toluidine and *o*-anisidine are listed on the following (Galleria Chemica):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products.
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain.

In addition o-toluidine is listed in the Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist") under the entry 'Toluidines, their isomers, salts and halogenated and sulfonated derivatives'.

Substance summary

Table 1.9A: Substance summary

Property	*o*-Toluidine	*o*-Anisidine
CAS No.	95-53-4	90-04-0
CAS name	benzenamine, 2-methyl-	benzenamine, 2-methoxy-
IUPAC and/or common and/or other names	*o*-toluidine	*o*-anisidine
Chemical structure		
Molecular formula	C_7H_9N	C_7H_9NO
Molecular weight	107.16 g/mol	123.15 g/mol

The following toxicology information was extracted from the NICNAS assessment report for *o*-toluidine[13] and *o*-anisidine.[14]

Table 1.9B: Acute toxicity end-points for *o*-toluidine

Toxicity	Species	Outcome	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats	750*	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	rabbit	3250	Schedule 5
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	rats	3800*	Schedule 5/6

[13] Publicly available on the NICNAS website at: https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1158

[14] Publicly available on the NICNAS website at: https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=1161

Skin irritation	Rabbit	Slight irritant	Schedule 5
Eye irritation	Rabbit	irritant	Schedule 6
Skin sensitisation		Limited data	N/A

* Methaemoglobinaemia has been observed in cats and humans at relatively low doses

Table 1.9C: Acute toxicity end-points for *o*-anisidine

Toxicity	Species	Outcome	SPF (2015) Classification
Acute oral toxicity LD_{50} (mg/kg bw)	Rats	1505–1890*	Schedule 6
Acute dermal toxicity LD_{50} (mg/kg bw)	Rats	>2000	Schedule 5
Acute inhalational toxicity LC_{50} (mg/m^3/4h)	Rats	>3870	Schedule 5
Skin irritation	Rabbits	Slight irritant	Schedule 5
Eye irritation	Rabbits	Slight irritant	Schedule 5
Skin sensitisation	local lymph node assay (LLNA) and guinea pig maximisation test (GPMT)	Equivocal	N/A

* Methaemoglobinaemia has been observed in cats and other species at relatively low doses

Acute toxicity, skin irritation and sensitisation

Refer to tables 1.9B and 1.9C.

Repeat-dose toxicity

The toxic effects of the *o*-toluidine have been investigated in several sub-chronic and chronic repeated dose oral toxicity studies. The results demonstrated not only chemically-induced development of tumours (see carcinogenicity section), but also non-cancer effects. The sub-chronic studies, whilst limited by poor documentation or a single dose test concentration, demonstrated consistent effects with the targets for toxicity being the blood, liver, kidney, spleen and urinary bladder. A no observed adverse effect level (NOAEL) value could not be established with a lowest observed adverse effect level (LOAEL) for effects on the blood of 24 mg/kg bw/day in a 14-day study.

The toxic effects of *o*-anisidine from repeated oral exposure were investigated in a number of well-conducted studies (OECD TG 407) in Fischer 344, Wistar rats, and B6C3F1 mice. The results demonstrated not only chemically-induced development of tumours (see Carcinogenicity section), but also non-cancerous effects. The lowest observed adverse effect level (LOAEL) available from the 28-day study in rats was 80 mg/kg bw/day. The targets for toxicity are the bone marrow and spleen.

Genotoxicity

o-Toluidine is considered mutagenic based on the weight of evidence from available, well-documented in vitro and in vivo studies. The chemical was recommended for classification as a category 2 (1B for GHS) mutagenic substance). The chemical has been reported to cause mutations, DNA and chromosomal damage and cell transformation. o-Toluidine was reported to induce DNA lesions in different organs of exposed rats (liver, bladder) and mice (liver, bladder and brain. Furthermore, inhibited testicular DNA synthesis was reported in male mice following oral intubation. Renal DNA

synthesis was also inhibited after a single intraperitoneal injection of the lethal doses of the chemical in the suckling mice.

o-Anisidine classified or as hazardous (Category 3 mutagenic substance) with the risk phrase 'Possible risk of irreversible effects' (Xn; R68) The genotoxic and mutagenic potentials of the chemicals were evaluated in several well-conducted in vitro and in vivo studies. DNA adducts derived from the N-hydroxylated metabolite have been detected in both *in vitro* and *in vivo* (i.p. route of administration) studies.

Carcinogenicity

o-Toluidine

o-Toluidine is currently classified as hazardous (Category 2 carcinogen) with the risk phrase 'May cause cancer' (T; R45) in HSIS (Safe Work Australia). The available epidemiological data support an amendment to this classification to a Category 1 carcinogen.

The carcinogenicity of the hydrochloride salt (not listed on the AICS) was investigated in a number of well-conducted OECD TG 452-compliant oral studies (feeding) in male and female F344 and CD-1 rats and mice (B6C3F1 and CD-1). In addition to reduced bodyweight and survival, significant increases in the incidence of multi-organ benign and/or malignant tumours were reported in mice and rats exposed to 3000–16000 ppm of the chemical over three months to two years. The equivalent intake doses were calculated at 130–800 mg/kg bw/day. In rats, tumours were found in the spleen, scrotum, urinary bladder, mammary glands, liver, skin, abdominal cavity and blood vessels of the chemically-exposed animals. In mice, hepatocellular carcinomas, adenomas, haemangiosarcomas, abdominal haemangiosarcomas and haemangiomas were observed.

In humans, findings derived from several cohort studies of workers provide strong evidence for an increased risk of urinary bladder cancer associated with long-term occupational exposure to *o*-toluidine. The chemical is listed in the National Toxicology Program (NTP) Report on Carcinogens (Twelfth Edition) as 'reasonably anticipated to be a human carcinogen' (NTP, 2011). The International Agency for Research on Cancer (IARC) has reviewed epidemiological data and subsequently concluded that it is 'carcinogenic to humans' (Group 1) (IARC, 2010; IARC, 2012).

The mechanism of action underlying the carcinogenicity of *o*-toluidine is not fully understood, although it is considered to involve metabolic activation, DNA adduct formation and induction of DNA-damaging effects. A mechanism which includes genotoxicity is suspected.

o-Anisidine

o-Anisidine is currently classified as hazardous (Category 2 carcinogen) with the risk phrase 'May cause cancer' (T; R45) in HSIS (Safe Work Australia). The available data support this classification.

Data from long-term carcinogenicity studies indicated that chronic exposure to o-anisidine in its hydrochloride form, CAS No.134-29-2 (not listed on the Australian Inventory of Chemical Substances) produced malignant and benign tumours, particularly in the urinary bladder of rats and mice.

Chronic oral exposure of F344 rats and B6C3F1 mice to *o*-anisidine and its hydrochloride salt for two years resulted in transitional-cell papillomas and carcinomas of the urinary bladder in both species. The doses tested were 5000 or 10000 ppm (average of 333 or 666 mg/kg bw/day) for rats and 2500 or 5000 ppm for mice (average of 214 or 428 mg/kg bw/day). A very rare form of tumour in the rat, leiomyosarcoma, was also observed in the urinary bladder of high dose animals. Kidney and thyroid gland cancer, including transitional cell carcinoma of the renal pelvis, follicular-cell adenoma and carcinoma, papillary cystadenoma, and cystadenocarcinoma, were also identified in rats. Cancer-related deaths occurred within 83–88 weeks in animals treated with 5000 or 10000 ppm of the chemical. Another study has indicated the tumour-promoting activity of the chemical.

No human case reports or epidemiological studies are available. The International Agency for Research on Cancer (IARC) overall evaluation is that *o*-anisidine is 'possibly carcinogenic to humans' (Group 2B).

The mechanism of action for carcinogenicity of the animal is not completely understood; although, both genotoxic and non-genotoxic modes of action are considered plausible. The formation of reactive species that are capable of binding to DNA has been observed. Results from a two-year carcinogenicity study suggested that the observed increased incidence of follicular-cell tumours in male Fischer 344 rats is a potential consequence of the inhibition of thyroid hormone formation, which is catalysed by the thyroid peroxidase.

Reproduction and developmental toxicity

Limited data are available.

Observation in humans

o-Toluidine

o-Toluidine is highly toxic to humans and can be absorbed via inhalation and through dermal contact. Exposed individuals have been reported to exhibit clinical signs of toxicity including methaemoglobinaemia, haematuria, renal and bladder irritation, physiological and psychological deficits. Severe intoxication was also observed in individuals exposed to 40 ppm of the chemical for 60 minutes.

Results from a patch test study in 40 dermatitis patients, known to be hypersensitive to p-phenylenediamine, indicated positive reactions in 25% of participants following exposure to *o*-toluidine in yellow paraffin.

Workers with chronic exposure to the *o*-toluidine have been reported to display anaemia, weight loss, anorexia, cyanosis, methaemoglobinaemia, skin lesions, and disturbance in the central nervous system such as headache, dizziness and confusion. Additionally, haemoglobin adducts were found in the urine of workers exposed to the chemical, where higher levels were identified in those with existing impaired skin condition. These adducts were also present in the blood of children with exposure to the chemical and in hairdressers with chronic exposure to hair dyes containing the chemical.

o-Anisidine

Complaints of headache and vertigo, increased sulfhaemoglobin and methaemoglobin, and frequent occurrence of Heinz bodies were reported in workers exposed to o-anisidine (0.4 ppm (2 mg/m^3)).

Pre-meeting public submissions

One (1) pre-meeting submission was received in support. The main points were that the new schedule entry would be in alignment with international regulators in the EU, ASEAN and NZ.

Summary of ACCS advice to the delegate

The committee advised that new Schedule 10 entries be created for *o*-toluidine and *o*-anisidine for use in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows as follows:

Schedule 10 – New Entries

o-TOLUIDINE in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows.

o-ANISIDINE in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows.

The committee also recommended an implementation date of **1 June 2017**.

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

The reasons for the advice comprised the following:

- *o*-Toluidine and *o*-anisidine are used in tattoo inks and hair colourants.
- *o*-Toluidine and *o*-anisidine are genotoxic and carcinogenic.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACCS advice
- Public Submissions received
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is to create new Schedule 10 entries for *o*-toluidine and *o*-anisidine for use in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows.

The proposed wording for the schedule entries is as follows:

> **Schedule 10 – New Entries**
>
> *o*-TOLUIDINE in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows.
>
> *o*-ANISIDINE in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows.

The proposed implementation date of **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (b) the purposes for which a substance is to be used and the extent of use of a substance; and (c) the toxicity of a substance.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- *o*-Toluidine and *o*-anisidine are used in tattoo inks and hair colourants.
- *o*-Toluidine and *o*-anisidine are genotoxic and carcinogenic.

Public submissions on the interim decision

One (1) public submission was received that generally supported the interim decision, but proposed amendments. The main points of concern were:

- The derivatives should be excluded from the schedule entries for *o*-toluidine and *o*-anisidine.
  - A derivative of *o*-toluidine, Basic Violet 2 (currently unscheduled in Australia), is allowed as a colourant in cosmetic products in the EU (included in Annex IV of the Cosmetics Regulation) and is used in a variety of hair products in Australia – both as a hair dye and as a colourant in shampoos and conditioners. The schedule entry for *o*-toluidine will have unintentional consequences on products containing Basic Violet 2, which will no longer be able to remain on the Australian market. Basic Violet 2 is listed on the AICS but has not been assessed by NICNAS through their IMAP Assessment. The EU SCCS opinion for Basic Violet 2 in cosmetics recognises

the presence of *o*-toluidine as a category 1B carcinogen but that low concentrations would be of 'no concern in a hair dye formulation'.[15]

- The appropriateness of the proposed 'earliest possible implementation date' of 1 June 2017. The submission stresses that an adequate transition period of at least 12 months must be allowed for any labelling changes and/or reformulation that may be required where no immediate risk has been identified; and that there is no evidence to suggest immediate action is required for the risk management of this substance.

Delegate's final decision

The delegate's final decision is to create new Schedule 10 entries for *o*-toluidine and *o*-anisidine (excluding derivatives) for use in preparations for skin colouration with a concentration cut-off of 0.001 per cent or less as follows:

Schedule 10 – New Entries

o-TOLUIDINE (excluding derivatives) in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows **except** in preparations containing 0.001 per cent or less of o toluidine.

o-ANISIDINE (excluding derivatives) in preparations for skin colouration (including tattooing) and dyeing of hair, eyelashes or eyebrows **except** in preparations containing 0.001 per cent or less of o anisidine.

The implementation date has been extended to **1 February 2018.**

The delegate confirms that the reasons for the final decision are the same as those provided from the interim decision. Additional reasons for the final decision include:

- The delegate agrees with the submission that the entries for *o*-toluidine and *o*-anisidine should exclude derivatives.
- The delegate notes that *o*-toluidine is present as an impurity in cosmetic preparations of Basic Violet 1 at 0.001 per cent.[16] Dermal exposure to 0.001 per cent of *o*-toluidine is expected to be safe.
- The delegate notes that a longer implementation time is required to allow for labelling changes and/or reformulation.

[15] Basic Violet 2 COLIPA n° B115 available at https://ec.europa.eu/health/scientific_committees/consumer_safety/sccs_09-13/opinions_en

[16] Basic Violet 2 COLIPA n° B115 available at https://ec.europa.eu/health/scientific_committees/consumer_safety/sccs_09-13/opinions_en

2. Joint Advisory Committee on Chemicals and Medicines Scheduling (ACCS-ACMS #14)

Summary of delegate's final decisions

Substance	Interim decision
Nicotine	The delegates' final decision is that the current scheduling of nicotine remains appropriate.
Pentobarbital (pentobarbitone)	The delegates' final decision is that the current scheduling of pentobarbital remains appropriate.
Cannabis, tetrahydrocannabinols and cannabidiol	The delegate has deferred making a final decision at this time regarding the possible rescheduling of cannabis. The deferral of a final decision will allow sufficient time for the delegate to thoroughly consider all public submissions on the interim decision, including two late submissions. Further information on the final decision regarding the possible rescheduling of cannabis is likely to be provided by late May 2017. Should the final decision be released at this time and require an implementation date, it will be announced at the time of publication.
Epidermal Growth Factor	The delegates' final decision is that the current scheduling of epidermal growth factor remains appropriate.

Substance	Interim decision
Fennel Oil	**Schedule 5 – New Entry** FENNEL OIL **except**: a) in medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert and compliant with the requirements of the Medicines Advisory Statements Specification; b) in preparations other than medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert, and labelled with the warning: KEEP OUT OF REACH OF CHILDREN; or c) in preparations containing 5 per cent or less of methyl chavicol. **Appendix E, Part 2 – New Entry** FENNEL OIL Standard Statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once).), G3 (If swallowed, do NOT induce vomiting) **Part 2, Section 2.4 Child-resistant closures – New Entry** **Column 1, Name of the poison:** Fennel oil when included in Schedule 5. **Column 2, Nominal capacity**: 200 millilitres or less Implementation date of **1 June 2017**.

2.1 Nicotine

Referred scheduling proposal

An applicant has proposed to exempt nicotine from Schedule 7 at concentrations of 3.6 per cent or less of nicotine for self-administration with an electronic nicotine delivery system ('personal vaporiser' or 'electronic cigarette') for the purpose of tobacco harm reduction.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 7 – Proposed amendment

NICOTINE **except**:

a) when included in Schedule 6;

b) in preparations for human therapeutic use; or

c) in tobacco prepared and packed for smoking; or

d) in preparations for use as a substitute for tobacco when packed and labelled:

i) for use in an electronic nicotine delivery system (ENDS)

ii) nicotine concentration up to 3.6%

iii) maximum nicotine per container: 900 mg

iv) in a child resistant container

v) labelled with the concentration of nicotine and other ingredients

vi) labelled with the statement 'Keep out of reach of children'

vii) labelled with the statement 'Not to be sold to a person under the age of 18 years'.

The applicant's reasons for the request are as follows:

- Harm reduction is a well-documented strategy to reduce the harm of behaviour by substituting it with a less harmful behaviour. Tobacco harm reduction provides an alternative pathway for smokers who are unable or unwilling to quit nicotine. Tobacco harm reduction has huge potential to prevent death and disability from tobacco and reduce health inequalities.
- The scheduling of nicotine was considered by the National Drugs and Poisons committee (NDPSC) in October 2008. The proposed amendment was to exclude nicotine from Schedule 7 'in electronic cigarettes prepared and packed as an alternative to traditional smoking'. The committee agreed that the current scheduling remained appropriate and that the Schedule 7 parent entry for nicotine should remain unchanged (NDPSC Oct 2008).
- The applicant asserts since that earlier consideration there has been considerable development in the public health understanding, smoker adoption and regulation of these products globally. This application will update the committee on these developments, with the conclusion that the scheduling of nicotine in Australia for non-therapeutic purposes should be amended.

Current scheduling status

Nicotine is currently listed in the Poisons Standard in Schedules 7, 6 and 4, Appendix F (Part 3), and Appendix J (Part 2) as follows:

Schedule 7

NICOTINE **except**:

a) when included in Schedule 6;

b) in preparations for human therapeutic use; or

c) in tobacco prepared and packed for smoking.

Schedule 6

NICOTINE in preparations containing 3 per cent or less of nicotine when labelled and packed for the treatment of animals.

Schedule 4

NICOTINE in preparations for human therapeutic use **except** for use as an aid in withdrawal from tobacco smoking in preparations for oromucosal or transdermal use.

Appendix F, Part 3 – NICOTINE **except** when in tobacco

Safety directions: 1 (Avoid contact with eyes), 4 (Avoid contact with skin).

Appendix J, Part 2 – NICOTINE

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

Relevant scheduling history

In June 1991, the Drugs and Poisons Schedule Standing committee (DPSSC) amended the Schedule 4 entry for nicotine to include all preparations (except Schedule 3 chewing tablets) which could be used as an aid in smoking cessation, containing between 2 and 4 mg of nicotine or roll-on devices with 0.65 per cent or less of nicotine e.g. transdermal patches.

In August 1993, the National Drugs and Poisons Schedule committee (NDPSC) rejected a proposal to have 2 mg sublingual tablets rescheduled from Schedule 3 to Schedule 2 and 4 mg sublingual tablets rescheduled from Schedule 4 to Schedule 3.

In November 1993, the NDPSC agreed that Schedule 4 remained appropriate for patch formulations. Subsequently, in November 1997, transdermal patches were included in Schedule 3.

In February 1997, the NDPSC rescheduled nicotine 2 mg chewable tablets to Schedule 2. However, committee decided that the higher dosage (4 mg) should only be rescheduled to Schedule 3 to facilitate the counselling of heavy smokers by a pharmacist.

In August 1998, the NDPSC agreed to the inclusion of nicotine gum and transdermal patches in Appendix H.

In November 1998, the NDPSC considered down-scheduling nicotine for inhalation, when packed in cartridges for use as an aid in withdrawal from tobacco smoking, from Schedule 4 to Schedule 3 and decided that Schedule 3 was appropriate. The NDPSC noted that this form of oral inhalation was similar in many respects to the chewing gum, being absorbed mainly in the mouth and throat. The data provided indicated that nicotine plasma levels obtained via the inhaler were similar to those obtained with the 2 mg chewing gum.

In February 1999, the NDPSC amended this Schedule 3 nicotine entry to 'Nicotine as an aid in withdrawal from tobacco smoking in preparations for inhalation or sublingual use'. In August 2001, the NDPSC agreed that nicotine lozenges would have a comparable safety profile to that of sublingual tablets, and so it was appropriate to also include lozenges in Schedule 3. Subsequently, lozenge-preparations were down scheduled to Schedule 2 in June 2003. In February 2002, nicotine inhalers were rescheduled from Schedule 3 to Schedule 2.

In February 2010, the NDPSC considered an application to broaden the exemptions for specified NRT buccal dosage formats i.e. chewing gum and lozenges, to buccal preparations in general. The NDPSC decided to only down-schedule oromucosal sprays and did not support an exemption for oromucosal preparations in general, noting that this could potentially include preparations such as mouthwashes. The NDPSC was of the opinion that there was insufficient data for such a broad exemption.

In June 2010, the NDPSC considered a post-meeting submission regarding the February 2010 decision to exempt nicotine preparations for oral mucosal spray use from scheduling. The committee confirmed the February 2010 resolution (2010/58-20) to amend the scheduling of nicotine to exempt oromucosal spray use as an aid in withdrawal from tobacco smoking. The committee agreed that this decision should be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument under these new arrangements with an implementation date of 1 September 2010.

In June 2011, the ACMS considered a proposal to amend the Schedule 4 entry to exempt from scheduling when used for human therapeutic use as an aid in withdrawal from tobacco smoking: (i) nicotine oromucosal film; and (ii) nicotine inhalation cartridges for oromucosal use. These proposed exemptions were similar to the exemptions for nicotine in chewing gums, lozenges, and preparations for sublingual, transdermal or oromucosal spray use when used as an aid in withdrawal from tobacco smoking.

ACMS advised that the Schedule 4 exemption for nicotine in preparations for human therapeutic use be extended to include all oromucosal use and include a definition for *oromucosal* in the Poisons Standard Part 1, Interpretation. The committee advised and the delegate agreed with the deletion of the Schedule 2 nicotine entry (i.e. all nicotine inhalation cartridge preparations for oromucosal use as aids in withdrawal from tobacco smoking would become exempt with any other inhalation

preparations for human therapeutic use being captured by Schedule 4). Further, the delegate extended the scheduling exemption for nicotine in preparations for human therapeutic use to include all oromucosal use (to harmonise with the New Zealand scheduling of nicotine for human therapeutic use). The decisions were implemented on 1 January 2012.

Australian regulatory information

Electronic Nicotine Delivery Systems (ENDS) are also known as e-cigarettes, personal vaporisers and vape pens. Nicotine for human consumption is listed in Schedule 4 in the Poisons Standard, except when used as an aid in the withdrawal from tobacco smoking in preparations intended for oromucosal or transdermal use (e.g. nicotine patches, gum or mouth sprays). Nicotine is in Schedule 7, except in preparations for human therapeutic use or in tobacco prepared and packed for smoking. There are no restrictions on importation, but individuals may commit an offence under state and territory laws when they take possession of, use or import nicotine.

In the states and territories, it is an offence to manufacture, sell or supply nicotine as Schedule 7 poison without a licence or specific authorisation. This means e-cigarettes containing nicotine cannot be sold in any Australian state or territory. Nicotine can be imported by an individual for use as an unapproved therapeutic good (e.g. a smoking cessation aid), but the importer must hold a prescription from an Australian registered medical practitioner and only import not more than 3 months' supply at any one time. The total quantity imported in a 12-month period cannot exceed 15 months' supply of the product at the maximum dose recommended by the manufacturer. The purchase and possession of nicotine by individuals are not regulated by Commonwealth legislation, except for importation as allowed under Commonwealth law.

Non-nicotine e-cigarettes are currently not regulated as a therapeutic good under the Commonwealth Therapeutic Goods Act. To date, none have been approved by the TGA for registration as a medical device.

In April 2015, the Commonwealth Department of Health engaged the University of Sydney (in partnership with the Cancer Council New South Wales) to explore options to minimise the risks associated with the marketing and use of ENDS in Australia. The project was initiated under the auspices of the Intergovernmental committee on Drugs (IGCD) which reports to the Australian Health Ministers Advisory Council Mental Health, Drug and Alcohol Principal committee. The IGCD nominated that the Department of Health act as the lead agency to oversee the project.

The outcomes of the project are to inform policy options for ENDS (with or without nicotine) that may be considered separately or in coordination by the Commonwealth, state and territory governments. The project is due to report in mid-2016. The Tobacco Control Policy Section has indicated that the report is imminent. However, the broader dissemination of the report will be a matter for the IGCD. At this time it is unknown when the IGCD will be meeting to discuss this report.

International regulations

UK: The 2016 UK guidance policy on regulation of e-cigarettes is available through the following link https://www.gov.uk/guidance/e-cigarettes-regulations-for-consumer-products.

NZ: In August 2016, the NZ Ministry of Health released a consultation document, considering policy options for the regulation of electronic cigarettes and agreeing in principle to allowing the sale of nicotine e-cigarettes as a consumer product. This consultation is at http://www.health.govt.nz/publication/policy-options-regulation-electronic-cigarettes-consultation-document.

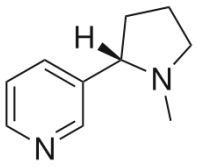
USA: The USA National Institute on Drug Abuse includes information on e-cigarettes at https://www.drugabuse.gov/publications/drugfacts/electronic-cigarettes-e-cigarettes.

Information on the US FDA ruling on e-cigarettes is available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm499234.htm and US FDA labelling information on vaporisers, e-cigarettes and ENDS is at http://www.fda.gov/tobaccoproducts/labeling/productsingredientscomponents/ucm456610.htm

Substance summary

Nicotine is a liquid alkaloid obtained from the dried leaves of the tobacco plant, *Nicotiana tabacum* and related species (Solanaceae). Tobacco leaves contain 0.5 to 8% of nicotine combined as malate or citrate. Nicotine is a colourless or brownish, volatile, hygroscopic, viscous liquid. Soluble in water and; miscible with dehydrated alcohol.

Table 2.1: Chemical information

Property	Nicotine
CAS No.	54-11-5
Chemical name	3-[(2*S*)-1-Methylpyrrolidin-2-yl]pyridine; (−)-1-Methyl-2-(3-pyridyl)pyrrolidine; (S)-3-(1-Methyl-2-pyrrolidinyl)pyridine
Chemical structure	
Molecular formula	$C_{10}H_{14}N_2$
Molecular weight	162.2 g/mol

When smoked, nicotine is distilled from burning tobacco and carried on tar droplets (particulate matter), which are inhaled. Nicotine has a plasma half-life of approximately 2 hours. It is metabolised in the liver primarily by the CYP2A6 enzyme into cotinine which is excreted by the kidneys. Nicotine used in nicotine solutions for e-cigarettes is extracted from tobacco leaves.

The toxicity of other ingredients inhaled in solutions used in e-cigarettes was not addressed in this application. The Applicant states that other chemicals in e-cigarette vapour include volatile organic compounds, carbonyls, aldehydes, tobacco-specific nitrosamines (TSNAs) and metal particles.

Pre-meeting public submissions

Of the 71 public submissions received, 54 supported and 17 opposed the proposal.

The 54 submissions in support of the proposal were from consumers (35), business owners or manufactures (6), peak bodies (2), advocacy groups (3), medical professionals (7) and a consultant (1).

The main points supporting the proposal were as follows:

- Personal accounts of quitting tobacco or reduced nicotine intake with positive health benefits using e-liquids containing nicotine when other nicotine therapies were unsuccessful or experienced side effects.
- International evidence that e-cigarettes reduce smoking and help smokers quit smoking. Consider that e-cigarettes work because they are pleasurable and address both the nicotine and habit aspect of smoking.
- Consumers can access harm reduction measures. Vaping is less harmful than smoking and is a significant harm reducer for smokers. Nicotine in ENDS may contain small amounts of other chemicals including volatile organic compounds, carbonyls, aldehydes, tobacco-specific nitrosamines (TSNAs) and metal particles. However, research indicates that they are present at much lower levels than in cigarette smoke. Use of ENDS reduces toxin intake.

- Nicotine is already approved in gums, lozenges, patches, inhalers and cigarettes.
- The current laws are confusing and mixed in Australia. Although the use of nicotine in vaping solutions is illegal, it is commonplace. Consumers struggle to understand why nicotine is hard to obtain, given cigarettes are easy to obtain. Suggest decriminalising possession of e-liquid nicotine, making it a consumer product at strength applied for in the application with availability through responsible retailers. By decriminalising, the risk associated with grey and black market unregulated supply chain would be mitigated.
- Consumers are concerned about importing products from overseas, the uncertainty of these products, the restrictions and breaking laws if vaping and potentially driving vaping consumers back to smoking as it is easier to go to the nearest store and obtain cigarettes.
- Consumers including minors can currently obtain e-liquid containing nicotine online from overseas, without responsible retailing to sell the products to adult consumers. Those without internet access and those uncomfortable with buying online are excluded from a harm reduction strategy which has been very successful for many people. As "disadvantaged groups in the population are more likely to take up and continue smoking" (Trends in the prevalence of smoking by socio-economic status), the very people who could be most helped by having low-strength nicotine available are those least likely to be able to access it.
- Suggestions were provided that these should have correct labelling displaying relevant consumer information and warnings relating to use e.g. unsuitability for pregnant and breast feeding women.
- The UK Royal College of Physicians report Nicotine Without Smoke: Tobacco Harm Reduction states 'A risk-averse, precautionary approach to e-cigarette regulation can be proposed as a means of minimizing the risk of avoidable harm, e.g. exposure to toxins in e-cigarette vapour, renormalisation, gateway progression to smoking, or other real or potential risks. However, if this approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking.' The UK Royal College of Physicians have stated that vaping is *at least* 95% safer than smoking and recommend doctors advising patients to switch to vaping.
- The Framework Convention on Tobacco Control Article 1(d) states: "tobacco control" means a range of supply, demand and harm reduction strategies that aim to improve the health of a population by eliminating or reducing their consumption of tobacco products and exposure to tobacco smoke; it seems that Australia is not fulfilling its FCTC obligations in providing access to the harm reduction strategies outlined in article 1(d).
- ENDS are available in New Zealand. Expected changes in New Zealand which would legalise availability of nicotine-containing e-liquids would likely create a problem with illicit product importation if Australia's regulations do not change. Consideration should be given to the emerging regulatory framework for e-cigarettes in New Zealand.
- Overseas these products are sold OTC – overseas research (UK) indicates that the majority of vapers are in ex-smokers and only 0.3% of never smokers used e-cigarettes in 2015 (similar to nicotine replacement therapy 0.1%). Public Health England has endorsed vaping as safer than smoking. Australia should harmonise with the UK, USA and NZ.
- In France, the High Council on Public Health has endorsed electronic cigarettes as a cessation tool.
- In Belgium the Superior Health Council has stated that electronic cigarettes are a less harmful alternative to tobacco (a position subsequently endorsed by the Health Ministry).
- In normal conditions of use, toxin levels in inhaled ENDS aerosol are below prescribed limit values for occupational exposure, in which case significant long-term harm is unlikely.
- Lethal overdose of nicotine is rare as nicotine is an emetic and any ingestion of liquid nicotine diluent, such as that used for ENDS would result in vomiting.

- Nicotine is the main psychoactive agent in tobacco, it has relatively minor health effects. It is not a carcinogen, does not cause respiratory disease and has only minor cardiovascular effects.
- Regarding the uptake of "vaping" in previously non-smoking youth, the available evidence does not support the "gateway hypothesis" that ENDS encourages nicotine addiction or uptake by youth. In the UK, daily ENDS use in youth is almost exclusively confined to those who already use combustible tobacco daily and regularly. Less than 0.2% of youth who have never smoked combustible tobacco have taken up vaping and there is no evidence of progression to smoking in this cohort.
- Abuse in children: as almost all minors who have used an e-cigarette with nicotinated e-liquid had also tried at least one cigarette. States that the majority of US youth who use vaporisers and e-cigarettes do not vape nicotine.
- Nicotine dependence in youth develops rapidly and over 50% of those youth who smoke daily are already nicotine dependent. Young people who are already smoking can reduce their harm by switching to ENDS by 95%, as was shown in the Public Health UK Report.
- Low concentration nicotine has a proven safety record and is currently widely available as Nicotine Replacement Therapy. The proposed low concentrations present no significant risks. Low risks can be mitigated by packaging and labelling requirements.
- Anti-tobacco restrictions should not be extrapolated to low concentration nicotine use.
- Many health professionals believe that the health risk of consuming nicotine in low dosages (as per electronic cigarettes) is about as harmful to your health as drinking a cup of coffee.
- One user has found the sweet flavours satisfy urges to eat sugary foods.
- No quantifiable harm for those in the vicinity of those vaping. Regarding second hand exposure concerns, at the Public Health UK report included that passive exposure to vapour have generally concluded that the risk to bystanders is very small and that Public Health England found that "ENDS release negligible levels of nicotine into ambient air with no health risks to bystanders".
- Australia's smoking rates amongst socially disadvantaged groups, particularly people with mental illness have remained unacceptably high. In the US, over 40% of tobacco sales are to people with a mental illness and this figure has been estimated to be even higher in Australia. Most of the 25-year mortality gap between people with schizophrenia and the general population is directly attributable to smoking. People with mental illness smoke in much higher rates than the general population, and the poor health outcomes reported in research are typically associated with smoking related harms. People with mental illness should be offered the opportunity to reduce or quit smoking using e-cigarettes. Existing nicotine replacement therapies have very poor efficacy and they are often costly, not at all affordable for people on a disability pension. E-cigarettes by comparison are very low cost, which increases the likelihood of their uptake by this population.
- Liquid nicotine should be supplied to agreed specifications in Australia by an accredited manufacturer and dispensed by an accredited Australian pharmacist. This would ensure a range of safeguards in regard to the supply and quality of nicotine in Australia
- In regard to the Personal Importation Scheme, the TGA website states "such therapeutic goods may not be approved for supply in Australia, and this means there are no guarantees about their safety or quality." Considers that this is an untenable situation in regard to a substance like liquid nicotine given emerging trends in e-cigarette use, vaping and smoking cessation considerations in Australia.
- There is a strong public health, ethical and pragmatic case to amend the schedule and to allow Australians access to much less risky ways to consume nicotine than smoking.
- Scientific evidence suggests negative effects of use in the long term are unlikely – significant drops (similar to cold turkey quitters) in biomarkers of smokers who switched to vaping. Stable, long term improvements in asthma symptoms have been found in smokers who switch to electronic cigarettes which demonstrate a significant level of harm reversal.

- The 3.6% is on the conservative side, some experts recommend stronger doses when attempting to quit nicotine altogether.
- Nicotine Quickmist® can be purchased at supermarkets and deliver 1 mg of nicotine per spray and each can has 150 sprays. These can be bought easily by anyone (even young adults).
- Nicotine toxicity has been misconceived in both popular press and general community perception, and even in some scientific sectors, with a lethal dose often quoted to be as little as 60 mg. Bernd Mayer[17] provides an historical perspective of this misconception, and provides a summary of research including clinical trials on animals, as well as investigations into inadvertent and intentional overdoses, and concludes that a careful estimate of the LD50 for nicotine is 0.5 g, or 6.5 mg/kg, which for the 36 mg/mL concentration proposed for approval, is theoretically approximately 15mL. But this would be almost impossible to reach the bloodstream in its entirety, due to the severe vomiting and diarrhoea such a dose would immediately arouse. Most recorded suicide attempts using nicotine have failed for this reason, with little or no long term effects.
- Vapers self-regulate nicotine dosage like smokers using tobacco products by reducing or stopping puffs taken on the basis of early symptoms of overdose such as headache, dizziness and nausea.
- Legalising nicotine-containing electronic cigarettes will make their manufacture, presentation and sale safer for consumers by:
  - reducing consumers' dependence on the unlawful or black market products proliferating in Australia
  - shaping a regulatory regime ensuring that all products on the market comply with appropriate standards of quality and safety
- The costs associated with listing nicotine vaping products on the ARTG is a disincentive to manufacturers to pursue with option of nicotine delivery.
- While the possession of nicotine solution remains illegal, there is no consumer regulation of these products – products are mislabelled to reduce detection. Current policy drives low-dose nicotine users underground, to obtain supplies from overseas or from merchants who do not label the nicotine content of the vaping fluid.
- Tax on e-cigarettes overseas is low compared to traditional cigarettes, this is incentive to switch
- ENDS has a 50-70% success rate of quitting tobacco smoking while having positive health effects on the body.
- Nicotine solution of 3.6% or less is also not enough product to cause a deadly result from ingestion as it takes 500-1000mg of pure Nicotine for death and the concentration level is too low.
- We should be making it easier, not harder, for people to access products that might help them quit, and provide more options.
- Potential for harm outweighs the potential for abuse
- One supporting submission also proposed a 3% allowance for animal use, moving it from Schedule 6 (Poison) to Schedule 5 (Caution) together with a Schedule 5 entry for nicotine in preparations containing 3.6% or less of nicotine when labelled and packed for use in e-cigarettes (electronic nicotine delivery systems or ENDS) on the basis that at the 3.6% level of dilution it should be used with caution, but it was not considered a dangerous poison.

The 17 submissions that do not support the proposal were from academia (1), Government Health Departments (7), non-government organisations (4) and peak bodies (5).

[17] Bernd Mayer. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch Toxicol. 2014; 88(1): 5–7: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3880486/

The main points opposing the proposal were as follows:

- The risks and benefits of the use of a substance
  - Given that nicotine is readily absorbed through the skin, nicotine available in liquid form for use in e-cigarettes poses a significant risk of acute nicotine poisoning. Furthermore, there is serious risk of acute nicotine poisoning for children which can occur through ingestion of products containing nicotine. There has been evidence of this internationally in the USA and UK.
  - The safety and long term health effects of these products are unknown, and any potential benefits are still to be determined and may be outweighed by the risks posed by their widespread use in the community.
  - The limited evidence to indicate that electronic cigarettes are effective nicotine cessation aids does not justify the risks posed by these products.
  - Research has shown that most people who use electronic cigarettes do not quit smoking conventional tobacco products, resulting in dual-use. Dual use results in a much smaller benefit on overall survival compared to quitting smoking entirely.
  - The chemical combinations used in electronic cigarettes have adverse impacts on pulmonary function and the cardiovascular system.
  - Second-hand e-cigarette vapour contains pollutants at levels above background levels and therefore is associated with negative health effects.
  - Nicotine is highly addictive. Permitting nicotine as an ingredient in e-cigarettes increases the risk of individuals, who would have otherwise been unlikely to become tobacco smokers, developing nicotine addiction.
  - The inherent risk of promoting ENDS as an option for smoking harm reduction follows the massive failures of past harm reduction interventions such as cigarette filters and 'light' and 'mild' product descriptors.
  - Through heavy marketing and advertising strategies, there is a possibility that smoking may once again become socially acceptable.
- The purposes for which a substance is to be used and the extent of use of a substance
  - There is limited and highly conflicting evidence internationally regarding the effectiveness of using e-cigarettes as a smoking cessation aid (with or without nicotine). This research is in its infancy with some research groups stating that smokers who used e-cigs were less likely to quit smoking tobacco than those who did not,[18] while others state that e-cigarettes helped smokers to stop smoking tobacco long term and reduce the amount smoked by half.[19]
  - Australia's National Health and Medical Research Council and the World Health Organization (WHO) does not currently consider e-cigarettes to be a legitimate tobacco cessation therapy as 'no rigorous peer-reviewed studies have been conducted to show that e-cigarettes are a safe, effective, Nicotine Replacement Therapy.
  - Availability of alternative smoking cessation aids, such as nicotine replacement therapies (e.g. gum and patches), have been rigorously assessed for efficacy and safety and have been approved by the TGA. However, e-cigarettes may be more attractive to smokers than existing nicotine replacement products, due to their lower cost, mimicry of the smoking action and potential better nicotine delivery system. These factors may discourage smokers from quitting.

[18] Grana *et al.* 'E-cigarettes: A Scientific review' *Circulation.* 2014, 129(19), 1972-1986 (Attachment G)

[19] McRobbie et al. 'Electronic cigarettes for smoking cessation (Review)' *Cochrane Database of Systematic Reviews*, 2016, 9, CD010216 (Attachment G)

- E-cigarettes containing nicotine may be marketed as a way to improve social status rather than for smoking cessation, which may increase the appeal of the product to non-tobacco-smoking youth.
- The extent of use of e-cigarettes containing nicotine is at the discretion of the user, which may increase the incidence of nicotine addiction and nicotine poisoning.
- Once a thorough assessment has been completed into the safety and efficacy of nicotine-containing e-cigarettes as a smoking cessation aid, these products should be restricted to prescription only.
- Evidence suggests that e-cigarettes undermine the intent of smoke-free laws, as many smokers use non-nicotine e-cigarettes in legislated smoke-free areas to maintain their smoking behaviour.

- The toxicity of a substance
  - Nicotine is highly toxic and poses a number of health hazards including adverse cardiovascular, respiratory, renal and reproductive effects. Despite the lower dose proposed, effects on cardiovascular system and the risk of developing cardiovascular and respiratory diseases are nearly as large as smoking traditional tobacco products.
  - Nicotine can be absorbed through the skin and poisoning may result in symptoms such as nausea, vomiting, seizures, abdominal pain, fluid build-up in the airways (bronchorrhea), high blood pressure, ataxia, rapid heart rate, headache, dizziness, confusion, agitation, restlessness, neuromuscular blockade, respiratory failure and death (with large doses – medium lethal dose 6.5-13 mg/kg).
  - Evidence from the International Agency for Research on Cancer (the WHO's source for information about cancer) suggests that nicotine is associated with DNA damage and other pathways of carcinogenesis.
  - Human and animal data suggest that nicotine exposure during periods of developmental vulnerability (foetal through adolescent stages) has multiple adverse health consequences, including impaired foetal brain and lung development, and altered development of cerebral cortex and hippocampus in adolescents, which may result have future mental health implications for the exposed child.
  - The claim that 'ENDS are 95% less harmful than smoking' was derived from the guesses of a consensus group (whose provenance has been heavily questioned), rather than from an appropriately conducted and peer-reviewed, scientific research study.

- The dosage, formulation, labelling, packaging and presentation of a substance
  - The wide variation in available devices and cartridge fluids make it difficult to quantify the safety of all e-cigarettes.
  - Exemption from scheduling may mean there will be less control over standards and quality control of preparations, labelling and packaging considerations and the application of warning statements.
  - There is a lack of evidence to support a safe dose. Some submitters suggest that the proposed 3.6% is too high. This concentration equates to approximately 36 mg of nicotine per ml of liquid, in comparison to the 13-30 mg of nicotine in a single cigarette. Furthermore, the dosage of nicotine administered through an e-cigarette, and frequency of use, is largely at the discretion of the user. These factors may lead to an increased incidence of addiction and poisoning, especially in children.
  - Labelling
    - It is important that health risks of nicotine be clearly labelled and that the packaging be childproof and not be designed to appeal to young people.

- Some e-liquids that do not list nicotine on the label have been found, upon scientific testing by State and Territory health authorities, to contain nicotine. The Australian Competition and Consumer Commission has recently commenced proceedings in the Federal Court against two a-cigarette retailers alleging false or misleading representations and misleading conduct by making statements on their websites that their ENDS products did not contain toxic chemicals

– Formulation

- Allowing open access to ENDS nicotine supplies will result in large-scale respiratory exposure to thousands of e-cigarette additives (such as propylene glycol, glycerol, ethylene glycol and flavourings) which have never been assessed for safety via inhalation in aerosol form (whether directly of via second-hand vapour).

- When heated, one of the common e-cigarette additives, propylene glycol, can form the carcinogenic derivative propylene oxide.

- Flavoured e-cigarettes (e.g. bubble gum, fruit and confectionary flavours), with or without nicotine content, could appeal to adolescents (leading to rapid uptake of tobacco smoking) and to children (leading to toxicity).

– Device safety

- There are concerns regarding device safety and a growing amount of global evidence to suggest that ENDs devices carry a risk of battery failure, low-quality materials, manufacturing flaws and malfunction, leading in some cases to explosions, fire and injury.

- The potential for abuse of a substance

  – The practice of 'vaping' a high volume of liquid in order to produce the biggest or most intricate cloud of vapour also creates a risk of inadvertent nicotine poisoning if the e-cigarette used contains nicotine.

- Any other matters that the Secretary considers necessary to protect public health

  – Personal Importation Scheme: A process already exists for individuals to import personal vaporisers and/or liquid nicotine for personal therapeutic use via the TGA's Personal Importation Scheme.[20]

  – Gateway to relapse: Risk of gateway to relapse. There is a risk that former tobacco smokers and nicotine addicts may relapse through the use of e-cigarettes containing nicotine.

  – Gateway to tobacco use (in adults and adolescents):

    - International evidence from the USA and UK, indicate that e-cigarettes (regardless of nicotine content) are being used by individuals as a gateway to tobacco use, triggering a new generation of smokers. There is a concern that advertising e-cigarettes will serve to reverse much of the progress that has been made to de-normalise, de-glamorise and reduce tobacco smoking in Australia.

    - There has been a rapid increase in the number of adolescents using e-cigarettes in the USA and UK. In the UK, 20% of British youths (aged 11-15) have used e-cigarettes, 73% of whom are non-smokers. This has been associated with higher incidences of users transitioning onto traditional cigarettes. The US stats indicate that e-cigarette use has increased four-fold in middle and high schoolers from 2011-2012 and that the continual fall in cigarette smoking that has been occurring since at least 1998, stopped in 2014 and 2015.

  – Industry bias:

[20] https://www.tga.gov.au/personal-importation-scheme

- The argument that nicotine is all but benign is often advanced by those highly conflicted by commercial interests involved in selling ENDS. Such arguments seldom note the findings of a large body of research into possible adverse effects arising from consumption of nicotine.
- The long term business model for the ENDS industry must involve seeing cohorts of young people take up vaping, regardless of protests from that industry to the contrary. In the UK where it is illegal to sell ENDS supplies to children, a recent report[21] found that 40% of ENDS retailers did so.

Summary of Joint ACCS-ACMS advice to the delegate

The committee advised that the current scheduling of nicotine remains appropriate.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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; (f) any other matters that the Secretary considers necessary to protect the public health

The reasons for the advice comprised the following:

- There is a risk of nicotine dependence associated with use of Electronic Nicotine Delivery System (ENDS). The potential for nicotine dependence is much higher with third generation ENDS and is greater than with the nicotine replacement therapy products marketed in Australia. In countries such as the USA where there has been more ready access to ENDS there is some evidence that ENDS use in never-smoking youth may increase the risk of subsequent initiation of cigarettes and other combustible products during the transition to adulthood when the purchase of tobacco products becomes legal. There is some dual use of conventional cigarettes and ENDS in smokers. There is a risk that ENDS will have a negative impact on tobacco control and may re-normalise smoking. If exempt from Schedule 7, availability of ENDS in children may cause an increase in smoking as they transition to adulthood, which raises public health concerns.
- There is little evidence regarding the safety of long term nicotine exposure via ENDS. Exposure to nicotine in adolescents may have long-term consequences for brain development, potentially leading to learning and anxiety disorders. The toxicity of long term exposure to nicotine delivered by ENDS is unknown. Long-term exposure to excipients via the ENDS route of exposure is uncertain.
- Nicotine can cause nausea, vomiting, convulsions, bronchorrhoea, high blood pressure, ataxia, tachycardia, headache, dizziness, confusion, agitation, restlessness, neuromuscular blockade, respiratory failure and death in overdose.
- The proposed maximum amount of 900 mg of nicotine per pack is within the estimated lower limit causing fatal outcome (500 mg to 1g). There have been reports of unintentional ingestion of ENDS liquid by children with severe outcomes in some cases. The proposed maximum concentration of 36 mg of nicotine per mL is high (the EU Tobacco Product Directive specifies a maximum concentration of 20 mg/mL). The amount of nicotine in 5 mL of a 3.6% solution in ENDS is 180 mg, which would likely cause significant toxicity in a young child (5 mL would be one swallow for a toddler). Child-resistant packaging would reduce the risk of unintentional exposure to the solution in children.
- ENDS is used for Tobacco Harm Reduction, assistance with cessation of smoking and for recreational use. Public health authorities have varying views about the benefits of ENDS to tobacco harm reduction and as an aid in smoking cessation. Currently about 9% of current smokers and recent quitters in Australia use ENDS. Excepting nicotine from Schedule 7 would likely result in increased nicotine exposure via ENDS (based on countries such as the UK and USA where these

[21] http://www.localgov.co.uk/Retailers-flout-laws-on-selling-e-cigarettes-to-children/41409

products are more widely available, and the increase in Australia in recent years). In the UK 19% of smokers and 8% of ex-smokers currently use ENDS.

- The use of a label warning statement 'not to be sold to a person under the age of 18 years' is not likely to be effective unless there is enforcement of this requirement. There is a risk there will be inappropriate marketing and advertising of nicotine for use with ENDS if nicotine for use with ENDS is exempted from Schedule 7.

Delegates' considerations

The delegates considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACCS-ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegates' interim decision

The delegates' interim decision is that the current scheduling of nicotine remains appropriate.

The delegates considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the interim decision are the following:

- The delegates acknowledge and agree with the ACCS-ACMS advice.
- There is a risk of nicotine dependence associated with use of Electronic Nicotine Delivery System (ENDS). The potential for nicotine dependence is much higher with third generation ENDS and is greater than with the nicotine replacement therapy products marketed in Australia. In countries such as the USA where there has been more ready access to ENDS there is some evidence that ENDS use in never-smoking youth may increase the risk of subsequent initiation of cigarettes and other combustible products during the transition to adulthood when the purchase of tobacco products becomes legal. There is some dual use of conventional cigarettes and ENDS in smokers. There are several published studies showing that youth who initiate smoking with e-cigarettes are about three times more likely to be smoking conventional cigarettes a year later. There is a risk that ENDS will have a negative impact on tobacco control and may re-normalise smoking. If exempt from Schedule 7, availability of ENDS in children may cause an increase in smoking as they transition to adulthood, which raises public health concerns.
- There is little evidence regarding the safety of long term nicotine exposure via ENDS. Exposure to nicotine in adolescents may have long-term consequences for brain development, potentially leading to learning and anxiety disorders. The toxicity of long term exposure to nicotine delivered by ENDS is unknown. Long-term exposure to excipients via the ENDS route of exposure is uncertain.
- Nicotine can cause nausea, vomiting, convulsions, bronchorrhoea, high blood pressure, ataxia, tachycardia, headache, dizziness, confusion, agitation, restlessness, neuromuscular blockade, respiratory failure and death in overdose.

- The dosage, formulation, labelling, packaging and presentation of the nicotine as would occur if the scheduling was amended would allow nicotine to be too accessible as a liquid which has higher risks and requires appropriate controls.

- The proposed maximum amount of 900 mg of nicotine per pack is within the estimated lower limit causing fatal outcome (500 mg to 1g). There have been reports of unintentional ingestion of ENDS liquid by children with severe outcomes in some cases. The proposed maximum concentration of 36 mg of nicotine per mL is high (the EU Tobacco Product Directive specifies a maximum concentration of 20 mg/mL). The amount of nicotine in 5 mL of a 3.6% solution in ENDS is 180 mg, which would likely cause significant toxicity in a young child (5 mL would be one swallow for a toddler). Child-resistant packaging would reduce the risk of unintentional exposure to the solution in children.

- In the USA, accidental poisonings associated with e-cigarettes have increased from one per month in 2010 to 215 per month in 2014 including one death.

- ENDS is used for Tobacco Harm Reduction, assistance with cessation of smoking and for recreational use. Public health authorities have varying views about the benefits of ENDS to tobacco harm reduction and as an aid in smoking cessation. Currently about 9% of current smokers and recent quitters in Australia use ENDS. Excepting nicotine from Schedule 7 would likely result in increased nicotine exposure via ENDS (based on countries such as the UK and USA where these products are more widely available, and the increase in Australia in recent years). In the UK 19% of smokers and 8% of ex-smokers currently use ENDS.

- The use of a label warning statement 'not to be sold to a person under the age of 18 years' is not likely to be effective unless there is enforcement of this requirement. There is a risk there will be inappropriate marketing and advertising of nicotine for use with ENDS if nicotine for use with ENDS is exempted from Schedule 7.

Public submissions on the interim decision

Twenty-one (21) submissions were received. Five supported and 16 opposed the delegate's interim decision.

The main points in support of the proposal were as follows:

- There was support for the decision in light of the *2016 Surgeon General's Report: E-cigarette Use Among Youth and Young Adults*.[22] This report makes several conclusions:
  - E-cigarette use among youth and young adults is a public health concern, being the most popular tobacco product among youth.
  - E-cigarette use strongly associated with tobacco products.
  - Nicotine-containing products, in any form, among youth, are unsafe.
  - E-cigarette aerosol is not harmless and can contain harmful ingredients.
  - Other actions can be taken to reduce tobacco use among youth.
- Reiteration of the points made in pre-meeting consultation included:
  - Allowing open access to ENDS nicotine supplies will result in large-scale respiratory exposure to thousands of e-cigarette additives (such as propylene glycol, glycerol, ethylene glycol and flavourings) which have never been assessed for safety via inhalation in aerosol form (whether directly of via second-hand vapour).
  - When heated, one of the common e-cigarette additives, propylene glycol, can form the carcinogenic derivative propylene oxide.

[22] https://www.cdc.gov/tobacco/data_statistics/sgr/e-cigarettes/pdfs/2016_sgr_entire_report_508.pdf

  - Flavoured e-cigarettes (e.g. bubble gum, fruit and confectionary flavours), with or without nicotine content, could appeal to adolescents (leading to rapid uptake of tobacco smoking) and to children (leading to toxicity).

- The current scheduling remains appropriate and is in line with Australia's obligations under the WHO Framework Convention on Tobacco Control for the prevention and reduction in nicotine addiction.

- The emerging use of 'dripping', particularly in youth in the US, is of concern due to the user being exposed to higher nicotine levels than those with ENDS use.

- Recent studies since the initiation of public consultation support the interim decision, stating that ENDS use is associated with increased cardiovascular risk, e-liquids may have acute cytotoxic effects on respiratory cells and that ENDS use in youth in the US is on the rise.

The main points in opposition to the proposal were as follows:

- Traditional methods to quit smoking are ineffective. Prescription medicines are not viable due to side effects. Nicotine-containing fluid for e-cigarettes has been successful in quitting; recommends e-cigarettes to other smokers as an effective form of quitting.

- E-cigarettes are cheaper than tobacco.

- E-cigarettes are legal in several jurisdiction in the EU and USA and being considered in others. Australian smokers deserve the same opportunities to reduce their health risks as Europeans or Americans. Consumers demand practical workable regulation of low strength nicotine.

- There is already demand for e-cigarettes in Australia despite the lack of marketing the illegality of nicotine-containing liquid without prescription. Current smokers are obtaining nicotine-containing liquid illegally to combat addiction to tobacco and prohibition is not working. A regulated solution would lessen potential harm of nicotine-containing liquid of e-cigarettes. Concerns regarding nicotine overdosing can be managed through proper regulation.

- The lowest smoking rates in the world are in the countries where e-cigarettes are an alternative nicotine delivery method. Rates of tobacco use will not be able to fall substantially without proper regulation and permission of nicotine in e-cigarettes.

- The benefits of e-cigarettes outweigh the risks. Health risks associated with tobacco come from tar, rather than nicotine. Nicotine in use of ENDS enables a harm-reduction opportunity from smoking-related morbidity and mortality.

- "Dual use" in many cases is a transition stage and not a means to an end.

- Vapers self-regulate and cease when they sense they have had enough nicotine.

- Use of ENDS is supported by Royal College of Physicians and Public Health England. There is a lack of evidence on the safety of long term nicotine exposure via ENDS. Some evidence shows that those who use e-cigarettes over a six month period have fare less toxic and cancer-causing substances than those who use tobacco.

- Rejection of the assertion that use of ENDS leads to tobacco use among youth, based on several studies from the UK. There is evidence that counters that cited in the interim decision that ENDS use in never-smoking youth increases the risk of tobacco use. If a child who wishes to smoke cannot access an ENDS then they will acquire a tobacco product instead.

- The evidence concerning youth use of e-cigarettes is misrepresented throughout the interim decision. There is no evidence anywhere of harmful gateway effects. Concerns over use of ENDS in youth and over marketing of ENDS can be easily addressed through appropriate restrictions and regulations

- The risks from low-concentrations liquid nicotine in child-proof containers are similar to other potentially poisonous household chemicals.

- Recommendation of child-resistant packaging to reduce potential risks of nicotine-containing e-cigarette liquid.
- The absolute rate of accidental poisonings from liquid nicotine preparations remains low, despite reports they have increased.
- There is enforceable socially-responsible advertising in the UK of ENDS and this should be incorporated into Australian consumer law.
- There is evidence characterising the physics and chemistry of e-cigarette aerosol and cigarette smoke. E-cigarettes create much lower exposures to toxic agents.
- There are no reports of overdoses among regular users. Accidental exposures do happen but they represent a manageable and minor detriment compared to the risks associated with smoking.
- It is unreasonable that one nicotine delivery system is favoured over others, particularly when one permitted system is tobacco. If there is concern, then no bias should be shown for one system over another.

Delegates' final decision

The delegates have confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegates' final decision is that the scheduling for nicotine remains appropriate.

Reasons for the final decision additional to those provided from the interim decision include:

- The delegates noted the submissions which included some new evidence in support of, and opposing the interim decision. The reasons for the final decision include those reasons for the interim decision and the below reasons as well.
- It is in line with the 2016 United States Surgeon General's Report: E-cigarette Use Among Youth and Young Adults released in December 2016 which makes several conclusions:
  - E-cigarette use among youth and young adults is a public health concern, being the most popular tobacco product among youth.
  - E-cigarette use strongly associated with tobacco products.
  - The use of Nicotine-containing products in any form in youth is unsafe.
  - E-cigarette aerosol is not harmless and can contain harmful ingredients.
  - Other actions can be taken to reduce tobacco use among youth.
- It is in line with Australia's obligations under the WHO Framework Convention on Tobacco Control for the prevention and reduction in nicotine addiction.
- The Public Health Association of Australia in its submission noted that:
  - *there have been further major reports (including from the US Surgeon General) and publications confirming its appropriateness and raising additional concerns about cardiovascular and other harms; impacts on children and young people; potential to trigger relapse among ex-smokers or those attempting to quit; dual use; cessation outcomes; and tobacco industry use of new products for promotional and lobbying purposes.*
- This was also noted by the Australian Council on Smoking and Health in its submission to the interim decision.
- The fact that e-cigarettes with nicotine are legal in some other jurisdictions in the EU and the USA are not reasons to make nicotine for use in e-cigarettes exempt in Australia, especially with the success in decreasing smoking in Australia without them.

- It is acknowledged there are divergent expert views on the availability of nicotine containing e-cigarettes as was well demonstrated in 2014 with the two letters to the then Director General of the WHO, Margaret Chan, which provided opposite views from a broad range of eminent public health specialists and in the submissions in the initial consultation and following the interim decision.
- Current government policy supports the cessation of smoking rather than harm reduction.
- That current smokers are obtaining nicotine-containing liquid illegally to combat addiction to tobacco is in itself not a valid reason to allow it to be accessed legally.
- It is still possible for an electronic nicotine delivery system to be approved by the TGA and included on the ARTG for use as an aid to cease smoking, hence giving access to those smokers who wish to cease.

2.2 Pentobarbital

Referred scheduling proposal

The delegate is considering up-scheduling pentobarbital (pentobarbitone) when packed and labelled for injection from Schedule 4 (Prescription Only Medicine or Prescription Animal Remedy) to Schedule 8 (Controlled Drug). This is due to the reported misuse of injectable pentobarbital and its involvement in suicides and whether the greater access control of Schedule 8 is more appropriate.

Scheduling application

This was a delegate-initiated application. The delegate's proposed amendments to the Poisons Standard are as follows:

Schedule 8 – Amend entry

PENTOBARBITAL ~~**except** when included in Schedule 4.~~

Schedule 4 – Delete entry

~~PENTOBARBITAL when packed and labelled for injection.~~

The delegate-initiated rescheduling proposal is due to the reported misuse of injectable pentobarbital and its involvement in suicides and whether the greater access control of Schedule 8 is more appropriate.

Current scheduling status

Pentobarbital is currently listed in Schedule 4, Schedule 8 and Appendix K, as follows:

Schedule 8

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

Schedule 4

PENTOBARBITAL when packed and labelled for injection.

Appendix K

PENTOBARBITAL

Index

PENTOBARBITAL

Schedule 8
Schedule 4
Appendix K

PENTOBARBITONE
cross reference: PENTOBARBITAL

Other barbiturates are currently listed in the Poisons Standard as follows:

- Schedule 8 (butobarbitone, cyclobarbitone, secbutobarbitone and quinalbarbitone) with Appendix K entries;
- Schedule 4 when packed and labelled for injection and Schedule 8 for other uses (amylobarbital);
- Schedule 4 (methylphenobarbital, phenobarbital, and barbiturates except when separately specified).

Relevant scheduling history

In January 1955, at the first meeting of the Poisons Schedule committee, barbituric acid was placed in Schedule 4, with concentrations of barbituric acid below 1% placed in Schedule 2.

In July 1968, the Poisons Schedule Sub-Committee (PSC) suggested that barbiturate tablets should be strip packed, following an article in the Medical Journal of Australia raising concern that some attempts at suicide could be avoided if barbiturate drugs were individually wrapped in tin foil, rather than packed in bottles.

In June 1980, the committee considered barbiturate scheduling, following media reports of proposed changes in NSW relating to availability and the Capital Territory Health Commission Deputy Chair's concerns around danger and abuse of barbiturates. The committee sought views of the Pharmaceutical Benefits Advisory committee (PBAC), the Department of Veterans' Affairs (DVA), Australian Drug Evaluation committee (ADEC) and the Medicines Advisory committee on the use of barbiturates in medical practice.

In November 1980, the committee considered a minute from the Secretary of the Dental Health committee listing pentobarbitone and other barbiturates as necessary for anaesthesia and conscious sedation in dental practice. Other views of the MAC were presented and included use in the treatment of cholestasis of pregnancy, management of jaundice and infantile colic. A direction from the Public Health Advisory committee (October 1980) meeting to PSC required examination of barbiturate use and advice on appropriate methods of control. It was agreed that ramifications of placing barbiturates in Schedule 8 would be considered at the next meeting.

In March 1981, the November 1980 meeting's proposal to retain barbiturate group of drugs in Schedule 4 for use to treat epilepsy and for anaesthesia and reclassify all other as Schedule 8 was considered. A consensus was not reached and the matter referred to the May 1981 meeting. Members were to raise the matter with their own Poisons Advisory committees.

In May 1981, the committee received correspondence from the WA Commissioner for Public Health indicating that the WA Poisons Advisory committee favoured tightening supplies of barbiturates rather than reclassification into Schedule 8. There was general agreement that barbiturates should be included in Appendix D. A final decision on barbiturates was deferred to the next meeting.

In August 1985, the committee was advised that Queensland intended to allocate many barbiturates to Schedule 8, with other states initiating legislation for Schedule 8 as well. In August 1985, the committee recommended that barbiturates be included in Schedule 8, with the original Schedule 4 remaining for parenterals [i.e. delivery by injection] during a phasing-in period [i.e. implementation date] of 6-12 months.

Schedule 4 - PENTOBARBITONE when packed and labelled for injection.

Schedule 8 - PENTOBARBITONE except when included in Schedule 4.

In November 1986, the committee noted ADEC's view that barbiturates were used as anticonvulsants and parenteral barbiturate formulations should be excluded from any Schedule 8 proposals. Members were informed of the Ministerial Council on Drug Strategy adopting the scheduling proposal (excluding barbiturate anticonvulsants from Schedule 8).

In February 1987, the TAS member reported changing the wording of the barbiturate entries so that they are similar to the Poisons Standard. WA reported that barbiturates have been S8 for some months now and barbiturate prescriptions were reported.

International regulations

USA

In the United States of America, pentobarbital (as a derivative of barbituric acid) is a Schedule III Controlled Substance, along with narcotics such as amphetamine and other substances such as nalorphine, glutethimide and anabolic steroids (https://www.law.cornell.edu/uscode/text/21/812), from 27 October 1970. Anabolic steroids and other chemicals including barbital and phenobarbital were added to Schedule III in 1990.

UN

While it is a Class III psychotropic substance of the United Nations Convention on Psychotropic Substances 1971, no country that is a signatory to the convention has prohibited its import (as of the 2016 edition of the Green List of the International Narcotics Control Board).

UK

It is a Class B Controlled Drug in the United Kingdom, from 1 January 1985. It is a Schedule IV Controlled Drug under the Controlled Drugs and Substances Act in Canada.

Substance summary

Barbiturates are substituted pyrimidine derivatives in which the common structure, barbituric acid, has no CNS activity. CNS activity is conferred by substituting alkyl, alkenyl or aryl groups on the pyrimidine ring. Barbiturates are primarily used as sedative hypnotics and also anticonvulsants in sub-hypnotic doses.

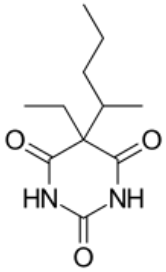
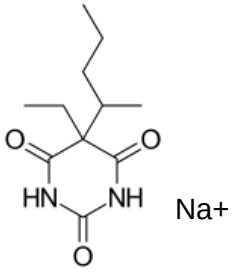
Short-acting barbiturates are well absorbed (primarily from the small intestine), with the onset of action being more rapid than with long- or intermediate-acting barbiturates.

The relative lipophilicity of each barbiturate determines the extent that they partition into fat. At steady state, the highest concentration of barbiturate in non-adipose tissue occurs in the liver and the kidney. The bio-transformation of most short-acting barbiturates occurs in the liver, where side-chains are oxidised to more polar and inactive compounds (e.g. alcohols, ketones, phenols or carboxylic acid) (Ellenhorn, 1988).

Pentobarbital is a short-acting barbiturate that is effective as an anaesthetic and euthanasia treatment for animals due to the nonselective central nervous system (CNS) depressant action. The sodium salt occurs as a white, slightly bitter powder which is freely soluble in water and alcohol but practically insoluble in benzene and ether (FDA, 2012).

Table 2.2: Chemical information

Property	Pentobarbital	Pentobarbital sodium
CAS Number	76-74-4	57-33-0
EC Number	200-983-8	200-323-9
IUPAC name	5-ethyl-5-(1-methylbutyl)-2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione	5-ethyl-5-(1-methylbutyl)-2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione sodium salt

Property	Pentobarbital	Pentobarbital sodium
Chemical structures		
Molecular formula	$C_{11}H_{18}N_2O_3$	$C_{11}H_{18}N_2NaO_3$
Molecular Weight	226.27 g/mol	249.26 g/mol
Other names	Pentobarbitone; 5-ethyl-5-(1-methylbutyl) barbituric acid; 5-ethyl-5-(sec-pentyl)barbituric acid; pentobarbituric acid; ethaminal; mebubarbital; NSC 28708; nembutal; neodorm	Sodium 5-ethyl-5-(1-methylbutyl) barbiturate; sodium 5-ethyl-4,6-dioxo-5-(pentan-2-yl)-1,4,5,6-tetrahydropyrimidin-2-olate; auropan; barpental; biosedan; butylone; diabutal; embutal; entobar; etaminal sodium; ethaminal sodium; euthanyl; euthatal; isobar; mebubarbital sodium; mebumal sodium; mebunat; NSC 10816; napental; narcoren; nembutal sodium; pacifan; pental; pentobarbital sodium; pentobarbitone sodium; pentonal; pentone; praecicalm; RS-pentobarbital sodium; sagatal; sodium 5-ethyl-5-(1-methylbutyl)barbiturate; sodium ethaminal; sodium Nembutal; sodium pental; sodium pentobarbital; sodium pentobarbitone; sodium pentobarbiturate; sodium-pent; soluble pentobarbital; somnopentyl; somnotol; sopental; sotyl; V-pento; vetbutal

Human Therapeutic names: Carbrital; Nembutal; Pentalgin (with codeine and paracetamol); and Pentobarbitone

Veterinary names: Valabarb Euthanasia Solution; Lethabarb Euthanasia Injection; Lethapharm Euthanasia Injection; Illium Pentobarbitone Sodium Anaesthetic Injection; and Euthanimal 40% Euthanasia Injection.

Pre-meeting public submissions

Of the 32 pre-meeting submissions received, 7 supported and 25 opposed the proposal.

The main points supporting the proposal were as follows:

- Support for all procedures that assist with the duty of care to staff.
- Agree pentobarbital should have stricter regulations for storage, particularly when the premises are unattended.
- Ease of current access is of concern.
- Some veterinarians already meet Schedule 8 requirements, or exceed Schedule 4 requirements for storage of pentobarbital.

- Veterinarians already maintain a register and have a safe for other Schedule 8 drugs, so this would not be a new process.
- Risk warrants additional licensing.
- Preference for locked cupboard or safe, without other Schedule 8 requirements.

The main points opposing the proposal were as follows:

- Pentobarbital is required for humane euthanasia of animals. Without easy access, there is the potential for animal welfare to be compromised.
- Concern there will be a compromise in animal welfare without reducing the number of suicides by veterinarians.
- Education around mental health is a more appropriate means of reducing suicide rates in veterinarians.
- Other lethal drugs are available as Schedule 4 poisons.
- Illicit trade in pentobarbital will still exist.
- Data provided shows low rate of suicides in Queensland between 2008-2010 attributable to barbiturates (0.3% in 2008-2010).
- Many reported deaths from pentobarbitone were from unknown sources or imported products.
- Current information on suicide using pentobarbital is limited and recommends a more detailed examination of the reported suicides to gain a better understanding of the issue.
- Moving to Schedule 8 will be onerous on veterinarians, both in requiring a larger Schedule 8 safe (cost involved) and in maintaining a register (more red tape).
- As euthanasia is traumatic for the vet, nurse and family, any register may not be accurate.
- Emotional burden currently shared with other authorised staff would be shifted to veterinarians.
- The size of the bottle (500 mL) is of concern. While this is practical for veterinary needs, it is not practical for storage and does not fit in existing Schedule 8 safes.
- Audit requirements won't necessarily catch diversion.
- The variable dose requirements for animal euthanasia would make skimming possible regardless of regulation.
- Increasing the Schedule 8 volumes controlled by the jurisdictions to accommodate the large quantities of pentobarbital would potentially loosen the control over other Schedule 8 drugs.
- Creates uncertainty in relation to transport and storage of pentobarbital in vehicles.
- Community groups would no longer have access, resulting in an increased diversion of injured animals to veterinary professionals to euthanase.
- Support for better storage however questions the need for Schedule 8.
- Pentobarbital be included in Schedule 4, Appendix D, mandating storage and record keeping rather than in Schedule 8.
- Schedule 4, Appendix D classification for pentobarbital already exists in some jurisdictions (e.g. NSW) or practices reflect it.
- Storage requirements that exceed those for Schedule 4 and are similar to Schedule 8 are already practiced in some organisations.

- Concern that meeting any veterinarian's Schedule 8 compliance requirements would involve the veterinary nurses. This is foreseen to place veterinary nurses in a difficult position.
- Pentobarbitone does not meet the factors for Controlled Drugs (Schedule 8) in the AHMAC Scheduling Policy for Medicines and Chemicals (1 February 2015).
- Requests a longer implementation date of at least 12 months if up scheduling occurs.
- Changes to packaging size and additional labelling in conjunction with access controls as an alternative to Schedule 8.
- Staff safety would be compromised in locations that required the transportation of sick and injured animals to external sites with veterinarians for euthanasia.
- Provision of exemptions requested if up scheduled to Schedule 8. To enable professional representative bodies and organisations to endorse non-veterinarians to be accredited in the access and use of pentobarbitone.

Summary of Joint ACCS-ACMS advice to the delegate

The committee advised that the current scheduling of pentobarbital remains appropriate.

The matters under subsection 52E (1) of the Therapeutic Goods Act 1989 considered relevant by the Committee included: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the advice comprised the following:

- Pentobarbital is not registered for use in humans. Narrow therapeutic window. Significant risk of Central nervous system (CNS)/respiratory depression.
- Benefits include cheap and efficient medicine for the humane euthanasia of animals in multiple settings. High mortality when used for self-harm purposes.
- Principal use is as an animal euthanasia product, for which it is the preferred agent and is widely used. The intended effect is death for animals that are suffering or have the potential to do so by central nervous system (CNS) and respiratory depression.
- Pentobarbital IV in 500 mL bottle is more widely used. This seems to be a major impediment to S8 because it does not fit into existing safes.
- There is potential for misuse for suicidal purposes. The lethal dose for humans is ~2-10 g.
- A wide range of authoritative organisations opposed the rescheduling on the basis of reasonable and practical grounds. Impact on suicide is unclear, but potentially low when considered in the entirety of suicides.

Delegates' considerations

The delegates considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACCS-ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegates' interim decision

The delegates' interim decision is that the current scheduling of pentobarbital remains appropriate and the delegates' recommend that that state and territory governments consider standardisation of the controls under their legislation.

The delegates considered the relevant matters under section 52E (1) of the Therapeutic Goods Act 1989: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the interim decision are the following:

- The delegates acknowledge and agree with the committee's advice.
- Pentobarbital is not registered for use in humans. It has a narrow therapeutic window and a significant risk of central nervous system (CNS)/respiratory depression. There is potential for misuse for suicidal purposes. The lethal dose for humans is approximately 2 10 grams
- Pentobarbital is a cheap and efficient medicine, and is the preferred agent and is widely used for the humane euthanasia of animals in multiple settings. The intended effect is death by CNS and respiratory depression for animals that are suffering.
- Pentobarbital in 500 mL bottles is widely used due to the large doses required (predominately in the field) to humanely euthanize large animals or multiple livestock. From a practical perspective, the delegates note that veterinarian access to parenteral solution of pentobarbital in 500ml bottles for field use is required and is consistent with the current schedule 4 entry.
- A wide range of authoritative organisations opposed the up-scheduling on the basis of reasonable and practical grounds. Impact on intentional suicide is unclear, but was thought to be low when considering the available data of suicides, and the people that were misusing pentobarbital for suicidal purposes.

Public submissions on the interim decision

One (1) submission was received in response to the interim decision. It was unclear whether the submission supported or opposed the interim decision. The submission included a transcript of a presentation by Hon Nick Goiran and Ms Elizabeth Storer and noted the following statement from the interim decision, 'Impact on intentional suicide is unclear, but was thought to be low when considering the available data of suicides, and the people that were misusing pentobarbital for suicidal purposes'.

Delegates' final decision

The delegates have confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegates' final decision is that the current scheduling for pentobarbital remains appropriate and that state and territory governments consider standardisation of the controls under their legislation.

Reasons for the final decision additional to those provided from the interim decision include:

- The delegates note the Queensland Coroner's Findings of Inquest in a case relating to a suicide involving pentobarbital delivered on 21 February 2017 and its recommendations. There was no new evidence provided in the findings to alter the interim decision.
- The delegates will write to all state and territory drugs and poisons units requesting they review and standardise the controls applied to the storage and access of Schedule 4 pentobarbital in their jurisdiction.

2.3 Cannabis

Referred scheduling proposal

The medicines scheduling delegate in view of the upcoming rescheduling of cannabis and tetrahydrocannabinols (THCs) proposes to consider:

> The final decision for cannabis provides for hemp seed oil to be exempt from Schedules 8 and 9 when the levels of total cannabinoids are 50 mg/kg or less.
>
> Due to further information provided after the publication of the final decision, the scheduling delegate is undertaking further consideration. This proposal seeks to determine whether this cut-off for total cannabinoids is appropriate for hemp seed oil, and the delegate is requesting additional information on the levels of cannabinoids (including tetrahydrocannabinols) in hemp seed oil. The delegate is also proposing to add to the cannabis entries regarding the hemp seed oil exception the following:
>
> "when labelled with either of the following warning statements:
>
> i. Not for internal use; or
>
> ii. Not to be taken."

Scheduling application

This was a delegate-initiated application. The delegate's proposed amendments to the Poisons Standard are as follows:

Schedule 9 – Amend entry

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

a) when separately specified in these Schedules; or

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

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

i) Not for internal use; or

ii) Not to be taken.

Schedule 8 – Amend entry

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

a) cultivated or produced, or in products manufactured[23], in accordance with the *Narcotic Drugs Act 1967*; and/or

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

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

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

except when:

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

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

ii) separately specified in Schedule 4; or

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

iv) in hemp seed oil for purposes other than internal human therapeutic use containing X mg/kg or less of cannabinoids when labelled with either of the following warning statements:

(A) Not for internal use; or

(B) Not to be taken.

Appendix D, Item 1

CANNABIS for human use.

Appendix K

CANNABIS

The delegate's reasons for the proposal is:

- Currently hemp seed oil has no restriction on cannabinoid content other than 50 mg/kg or less of tetrahydrocannabinols when labelled with either of the following warning statements:

  i. Not for internal use; or

  ii. Not to be taken

Current scheduling status

Cannabis and cannabinoids are currently listed in Schedules 4, 8 and 9, and in Appendix D and Appendix K.

Hemp seed oil is defined in the Interpretation of the Poisons Standard as follows:

PART 1 - INTERPRETATION

"**Hemp seed oil**" means the oil obtained by cold expression from the ripened fruits (seeds) of *Cannabis sativa*.

Following the 31 August 2016 final scheduling decision for cannabis and tetrahydrocannabinols to be implemented on 1 November 2016, the entries for cannabis, tetrahydrocannabinols and nabiximols will be listed in Schedules 8 and 9, and Appendix D and Appendix K as follows:

Schedule 9

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

a) when separately specified in these Schedules; or

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

c) in hemp seed oil for purposes other than internal human use containing 50 mg/kg or less of cannabinoids.[24]

[24] The November 2016 Poisons Standard contains an error, referring to 'cannabinols' instead of 'cannabinoids' under the Schedule 9 cannabis entry at item c. This will be corrected in the February 2017 update to be consistent with the August 2016 decision, pending the outcome of the advice of the committees.

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

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

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

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

    i) Not for internal use; or

    ii) Not to be taken; or

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

Schedule 8

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

a) cultivated or produced, or in products manufactured[25], in accordance with the *Narcotic Drugs Act 1967*; and/or

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

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

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

except when:

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

    ii) separately specified in Schedule 4; or

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

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

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

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

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

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

except when:

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

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

        (A) Not for internal use; or

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

(B) Not to be taken; or

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

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

NABIXIMOLS (botanical extract of *Cannabis sativa* which includes the following cannabinoids: tetrahydrocannabinols, cannabidiol, cannabinol, cannabigerol, cannabichromene, cannabidiolic acid, tetrahydrocannabinolic acids, tetrahydrocannabivarol, and cannabidivarol, where tetrahydrocannabinols and cannabidiol (in approximately equal proportions) comprise not less than 90 per cent of the total cannabinoid content) in a buccal spray for human therapeutic use.

Schedule 4

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

Appendix D, Item 1

CANNABIS for human use.

TETRAHYDROCANNABINOLS for human use.

Appendix K

CANNABIS

TETRAHYDROCANNABINOLS

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CANNABICHROMENE
cross reference: NABIXIMOLS, CANNABIS

CANNABIDIOL
cross reference: NABIXIMOLS, CANNABIS

CANNABIDIOLIC ACID
cross reference: NABIXIMOLS, CANNABIS

CANNABIDIVAROL
cross reference: NABIXIMOLS, CANNABIS

CANNABIGEROL
cross reference: NABIXIMOLS, CANNABIS

CANNABINOIDS
cross reference: NABIXIMOLS, CANNABIS, TETRAHYDROCANNABINOLS

CANNABINOL
cross reference: NABIXIMOLS, CANNABIS

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

TETRAHYDROCANNABINOLIC ACID
cross reference: NABIXIMOLS, TETRAHYDROCANNABINOLS

TETRAHYDROCANNABINOLS
cross reference: CANNABIS, HEMP SEED OIL, NABIXIMOLS

TETRAHYDROCANNABIDIVAROL
cross reference: NABIXIMOLS, TETRAHYDROCANNABINOLS

Relevant Scheduling History

Cannabis

In August 1999, the committee reviewed the status of its foreshadowed proposal to amend the Schedule 9 entry for cannabis to exempt from scheduling cannabis when grown commercially for fibre production and manufactured goods containing hemp fibre. It was seen that such a proposal would provide uniformity in controls exerted by state and territory governments. A general exemption for hemp fibre and hemp fibre products could be made. The committee considered a general exemption for hemp fibre and hemp fibre products could be made. The exemption would allow sale of such hemp fibre and manufactured products in all jurisdictions.

Tetrahydrocannabinols

In May 1998, the committee considered additional technical and regulatory information relating to a request to exempt from Schedule 9 tetrahydrocannabinols when in hemp seed oil and products for external use when containing 50 mg/kg or less of tetrahydrocannabinols (THC). The committee supported the proposal that hemp seed oil and products containing hemp seed oil should be exempt from the Schedule 9 entry for tetrahydrocannabinols when containing 50 mg/kg of THC and when for external use.

Nabiximols (sativex®)

In October 2009, the committee considered an entry specific for *Cannabis sativa* extract, nabiximols, after the issue was raised at the June 2009 meeting that certain jurisdictions were unable to allow SAS access to the substance as it was captured under Schedule 9. As discussed in June, the committee members agreed on the Schedule 8 listing. The committee also agreed that the Schedule 8 entry should limit the allowed presentation to buccal sprays as this would further reinforce the very restricted scope of this entry and would require any new presentation to be brought to the attention of the committee.

In May 2010, nabiximols were included in Schedule 8 and Appendices D and K. The committee advised that nabiximols needed to be added to Appendix D, Item 3 to limit access through SAS Category A. This addition would allow restricted access to nabiximols only, not to cannabis extracts, but would not prohibit use for clinical trials provided by an authorised prescriber only. The committee agreed to not restrict the Schedule 8 nabiximols entry by indication (for Multiple Sclerosis). Members additionally agreed that it would be appropriate to include nabiximols in Appendix K due to sedating effects.

In March 2013, the committee considered a proposal to reschedule nabiximols from Item 3 of Appendix D to Item 1 of Appendix D of the SUSMP and amended Appendix D to include the entry of nabiximols.

In August 2016, the delegate amended the nabiximols entry in line with the August 2016 decision for cannabis and tetrahydrocannabinols to use the plural ‘s’ for tetrahydrocannabinols and their acids.

Cannabis and tetrahydrocannabinols

In March 2016, the committee considered a proposal to amend the Schedule 9 entries and create new Schedule 8 entries for cannabis and tetrahydrocannabinols with Appendix D, Part 1 and Appendix K warnings. The committee supported the proposal and in August 2016, the Medicines Scheduling Delegate decided to amend the scheduling entries for cannabis, tetrahydrocannabinols and nabiximols, with an implementation date of 1 November 2016.

Minutes of these meetings are available on Govdex (Dashboard/Advisory committee on Medicines Scheduling/Meeting/Minutes).

Australian regulatory information

Narcotics Drugs Act and importation

Under the *Narcotic Drugs Act 1967* (the ND Act) a ‘drug’ includes all extracts of cannabis (including hemp) from cannabis plants.

The manufacture of a drug that includes (or is from) a cannabis plant, can only be authorised under a manufacture licence in limited circumstances under the ND Act. As outlined under Section 11K, the Secretary must refuse to grant a manufacture licence if not satisfied on reasonable grounds with one of the following (these are set out in paragraphs 11K(2)(b) and (c), respectively):

- that the drug is a medicinal cannabis product that will be:

  (i) supplied for the purposes of use in a clinical trials that is, or is likely to be approved under the *Therapeutic Goods Act 1989* (the TG Act) or notified to the Secretary under that Act; or;
  (ii) otherwise supplied in accordance with an approval or authority under the TG Act; or
  (iii) supplied by a pharmacist in a public hospital in accordance with the TG Act;

- that the drug is a medicinal cannabis product that is registered within the meaning of the TG Act under section 25 of that Act.

Therefore extracts of cannabis (or hemp), or the manufacture of drugs from cannabis plants, may only be for the purposes of the aforementioned activities.

Extracts for food, cosmetics, veterinary use (including pet food) are not permitted.

Cannabis, cannabinoids, cannabis resins, tetrahydrocannabinols, cannabis seeds, cannabis plants and parts of cannabis plants are prohibited imports under the Customs (Prohibited Imports) Regulations 1956. Cannabis and THCs that are in Schedule 9 will not be granted an import permit, unless a State or Territory Health Department agency also authorises/grants the applicant a permission to possess, hold or supply cannabis or THC listed under Schedule 9 of the current Poisons Standard.

Substance summary

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

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

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

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

Hemp seed oil as defined in Part 1 Interpretation, Paragraph (1) of the Poisons Standard is the oil obtained by cold expression from the ripened fruits (seeds) of *Cannabis sativa*. Hemp oil, is distinct from hemp seed oil and includes extracts from the flowering tops or leaves or any other part of the Cannabis plant other than the ripened fruit (seeds).

Information in the public domain, including websites and literature articles[26] report cannabinoids are not synthesised within the hemp seed. However, traces of delta-9-tetrahydrocannabinol and

[26] http://www.foodstandards.gov.au/code/proposals/Pages/P1042LowTHChemp.aspx and
Leizer, C. *et al.,* The Composition of Hemp Seed Oil and Its Potential as an Important Source of Nutrition, J. Nutraceuticals, Functional & Medical Foods *2000* 2(4) 35 – 53,
http://www.extsoilcrop.colostate.edu/CropVar/documents/oilseeds/alternative_oil/potential_of_hemp_seed_oil.pdf

cannabidiol contamination of the seed may occur due to residual contamination of the outside of the seed coat, even under good agricultural/manufacturing practice. Rigorous cleaning methods, including washing, sieving and shelling, may help reduce or remove any cannabinoid contamination of seeds.

Reported gas chromatography (GC) analytical composition data of hemp seed oil (variety Fedora-19) from Leizer, et al, (2000) includes significant portions of polyunsaturated fatty acids such as linoleic acid, oleic acid, stearic acid eichosanoic acids and palmitic acid, with more than 80% of the content being unsaturated fatty acids. Other trace compounds reported include Vitamin E (tocopherols), β-sitosterol, ad terpenes (e.g. myrcene and caryophyllene) and salicylates. Given this information, hemp seed oil products should not contain significant amounts of cannabinoids. The presence of cannabinoids in hemp seed oil is considered to arise from either a contamination or adulteration, rather than be naturally occurring.

Pre-meeting public submissions

Three (3) public submissions were received for cannabis. Of these, 2 were opposed to the proposed amendments, and one proposed an additional amendment. The main points were:

- Concern that the level of caution concerning cannabis and its constituents is far higher than warranted given the suggested therapeutic benefit;
- The US legislation is being approved to allow personal use in addition to medical use;
- Multiple studies show that CBD is safe, and it is not appropriate to set any limit in hemp seed oil;
- Concern that there is ambiguity in the current Schedule 9 entries for cannabis and tetrahydrocannabinols (THC) and that the scheduling of low-THC hemp and hemp seed oils should also be exempt (less than 50 mg/kg);
- Concern that products not intended for therapeutic use (e.g. cosmetics and dog food) will be captured in the Schedule 8 and Schedule 9 entries and whether this is appropriate;
- One submission proposed that Schedule 9 entries for cannabis and tetrahydrocannabinols both be amended to include the following entry: "d) in products for the purpose other than internal human consumption use containing 50 mg/kg or less of tetrahydrocannabinols".

Summary of Joint ACCS-ACMS advice to the delegate

The committee advised that the Schedule 9 and Schedule 8 entries for cannabis and Schedule 9 entry for tetrahydrocannabinols be amended as follows:

Schedule 9 – Proposed Amended Entry

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

a) when separately specified in these Schedules; or

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

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

i) Not for internal use; or

ii) Not to be taken.

d) in products for the purposes other than internal human use containing 20 mg/kg or less of tetrahydrocannabinols and 50 mg/kg or less of total cannabinoids.

Schedule 8 – Proposed Amended Entry

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

a) cultivated or produced, or in products manufactured[27], in accordance with the *Narcotic Drugs Act 1967*; and/or

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

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

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

except when:

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

i) separately specified in Schedule 4; or

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

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

(A) Not for internal use; or

(B) Not to be taken.

Schedule 9 – Proposed Amended Entry

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

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

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

c) in hemp seed oil, containing ~~50~~ 20 mg/kg or less of tetrahydrocannabinols and 50 mg/kg or less of total tetrahydrocannabinoids when labelled with either of the following warning statements:

i) Not for internal use; or

ii) Not to be taken; or

d) in products for purposes other than internal human use containing ~~50~~ 20 mg/kg or less of tetrahydrocannabinols and 50 mg/kg or less of total cannabinoids.

Schedule 8 –Proposed Amended Entry

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

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

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

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

except when:

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

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

ii) in hemp seed oil, containing ~~50~~ 20 mg/kg or less of tetrahydrocannabinols and 50 mg/kg or less of total cannabinoids when labelled with either of the following warning statements:

(A) Not for internal use; or

(B) Not to be taken; or

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

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

The committee recommended that the schedule entry for cannabidiol be amended in Schedule 4 of the Poisons Standard to include a consistent hemp seed oil exemption:

Schedule 4 – Proposed Amended Entry

CANNABIDIOL in preparations for therapeutic use containing 2 per cent or less of other cannabinoids found in cannabis, **except** when:

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

i) Not for internal use; or

ii) Not to be taken.

b) in products for the purposes other than internal human use containing 20 mg/kg or less of tetrahydrocannabinols and 50 mg/kg or less of total cannabinoids.

The committee recommended an implementation date of **1 June 2017**.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the advice comprised the following:

- There is low risk associated with the concentration of cannabinoids permitted under the exceptions.
- Hemp seed oil contains fatty acids considered useful as skin conditioners and topical use is low risk, particularly if the level of psychoactive cannabinoid is minimal.
- Low THC hemp seed oil has been used in cosmetic and pet food products. Limiting human use to 'external only' mitigates against risk of internal consumption of cannabinoids, particularly tetrahydrocannabinols and cannabidiol.
- The risk of toxicity is minimal in the concentrations permitted under the exceptions Most of the toxicity associated with cannabis is due to the tetrahydrocannabinols (THCs) content.
- The toxicity will be low if the THC content is low. International jurisdictions have cut-off limits lower than 50 mg/kg; some jurisdictions have as low as 10 mg/kg.
- Label warning statements 'not for internal use' or 'not to be taken' would apply and make it clear that the products are not for human internal use.

- Including specific instructions about "Not for internal use" and/or "Not to be taken" makes it clear that oral formulations are not exempted from scheduling.
- There does not appear to be any evidence of misuse or abuse of the products that currently contain low concentrations of tetrahydrocannabinols/cannabinoids.
- Limiting the tetrahydrocannabinols content for exemption from scheduling reduces the risk of abuse and diversion.
- The amendments to the schedule entries would provide clarity and avoid any ambiguity about the products intended to be captured.
- There is merit in having consistent exemptions across all cannabis and tetrahydrocannabinols entries in Schedules 8 and 9 and the Schedule 4 entry for cannabidiol.

Delegates' considerations

The delegates considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACCS-ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegates' interim decision

The delegates' interim decision is that:

a) the Schedule 8 and 9 entries for cannabis and tetrahydrocannabinols be amended to remove the text 'internal' relating to human use

b) the 'hemp seed oil' clauses in the Schedule 9 entries for cannabis and tetrahydrocannabinols be amended to:

   i) limit total cannabinoid content to 50 mg/kg including a new limit for tetrahydrocannabinols of 20 mg/kg

   i) restrict use in humans

   ii) include labelling with either of the following warning statements 'not for internal use' or 'not to be taken'

c) the Schedule 8 cannabis and tetrahydrocannabinols entries be amended by deleting the exemptions for 'hemp seed oil' and 'products'

d) the Schedule 9 entry for tetrahydrocannabinols be amended by deleting the exemption for 'products'

e) the Schedule 4 entry for cannabidiol be amended to include clarification in relation to total content of other cannabinoids.

The amended wording for the Schedule 8 and Schedule 9 entries for cannabis and tetrahydrocannabinols and the Schedule 4 entry for cannabidiol are as follows:

Schedule 9 – Amend Entry

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

a) when separately specified in these Schedules; or

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

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

i) Not for internal use; or

ii) Not to be taken.

Schedule 8 – Amend Entry

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

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

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

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

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

except when:

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

ii) separately specified in Schedule 4; or

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

Schedule 9 – Amend Entry

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

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

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

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

i) Not for internal use; or

ii) Not to be taken.

Schedule 8 – Amend Entry

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

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

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

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

except when:

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

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

Schedule 4 – Amend Entry

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

Appendix D, item 1 – Current entries

CANNABIS for human use.

TETRAHYDROCANNABINOLS for human use.

Appendix K – Current entries

CANNABIS

TETRAHYDROCANNABINOLS

The proposed implementation date is **1 June 2017.**

The delegates considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the interim decision are the following:

- The delegates acknowledge the committee's advice.
- There is low risk associated with the concentration of cannabinoids permitted under the exceptions. The toxicity will be low if the THC content is low. International jurisdictions have cut-off limits lower than 50 mg/kg; some jurisdictions have as low as 10 mg/kg.
- Low THC hemp seed oil has been used in cosmetic and pet food products. Limiting human use to 'external only' mitigates against risk of internal consumption of cannabinoids, particularly tetrahydrocannabinols and cannabidiol. Hemp seed oil contains fatty acids considered useful as skin conditioners and topical use is a low risk, particularly if the level of psychoactive cannabinoid is minimal.
- Label warning statements 'not for internal use' or 'not to be taken' would apply and make it clear the products are not for human internal use. Including specific instructions about "Not for internal use" and/or "Not to be taken" makes it clear that oral formulations are not exempted from scheduling.
- There does not appear to be any evidence of misuse or abuse of the products that currently contain low concentrations of tetrahydrocannabinols/cannabinoids. Limiting the tetrahydrocannabinols content for exemption from scheduling reduces the risk of abuse and diversion.
- The amendments to the schedule entries would provide clarity and avoid any ambiguity about the products intended to be captured. There is merit in having consistent exemptions across all cannabis and tetrahydrocannabinols entries in Schedules 8 and 9 and the Schedule 4 entry for cannabidiol, in particular the limits for total cannabinoids and tetrahydrocannabinols.

- The product exemption applying to products for purposes other than internal human use containing 50 mg/kg or less of tetrahydrocannabinols is being omitted as this is inconsistent with the operation of the *Narcotic Drugs Act 1967* (the ND Act) and may be breaching Australia's obligations under the Single Convention on Narcotic Drugs 1961(the Single Convention). Any manufacture of drugs would be regulated under ND Act, and would require the manufacturer to be holding a manufacture licence and a permit. In view of the recent amendments to the ND Act, the Secretary must refuse to grant a manufacture licence involving cannabis, unless satisfied on reasonable grounds that at least one of the circumstances set out in subsection 11K(2) of the ND Act is met. Thus the end use of the manufactured cannabis under the ND Act is limited for a person to be granted a manufacture licence, irrespective of the concentration of cannabis in the end product to be supplied. Similarly, the cultivation and production of cannabis or cannabis resins are regulated under the ND Act.

  – Any person who manufactures, cultivates cannabis plants or produces cannabis or cannabis resins without a licence may be committing an offence under the Criminal Code Act. Any importation of drugs would be regulated under the Customs (Prohibited Imports) Regulations 1956.

  – The Single Convention does not apply to the cultivation of cannabis plants exclusively for industrial purposes (fibre and seed) or horticultural purposes. However, it applies to the cultivation of cannabis plants for the production of cannabis or cannabis resins, and requires amongst others that the manufacture of drugs be under licence, subject to exemptions, and that trade in and distribution of drugs be under licence, subject to exemptions.

- The cannabidiol Schedule 4 entry covers only therapeutic use. Therefore non-therapeutic use falls under other Schedule entries for cannabis.

- The cannabidiol entry amendment is to clarify that the cannabidiol must contain at least 98 per cent cannabidiol relative to the total amount of other cannabinoids in the cannabidiol.

- Amending the Schedule 9 entries for cannabis and tetrahydrocannabinols to introduce specific limits for total cannabinoids including tetrahydrocannabinols.

- NICNAS have advised that there are no cannabinoids approved as ingredients in cosmetics (i.e. external human use). Therefore there is no requirement for an exemption, as no approved products exist. This would lead to removal of the exemptions for hemp seed oil from the tetrahydrocannabinols and cannabis Schedule 8 entries and removal of the exemptions for products from the tetrahydrocannabinols and cannabis Schedule 9 and Schedule 8 entries.

- Food is not considered as part of this decision.

Public submissions on the interim decision

One (1) submission was received and this opposed the interim decision. The main points of the submission were:

- The proposed amendments in the interim decision differ from those in the proposal, as well as from the current and previous entries for cannabis and tetrahydrocannabinols. The submission asserts that the interim decision will have an unjustified effect of capturing certain previously lawful products in Schedule 9.

- In light of recent and ongoing policy developments with respect to cannabis, the submission asserts that the committee and the scheduling delegates are rushing to implement changes to the Poisons Standard and are doing so without the requisite level of careful consideration and public consultation.

- The submission asserts that there are flaws in the changes to the existing exceptions and cannabinoid content limits proposed in the interim decision, and suggests that these should be the subject of wider industry consultation before any final decision is made.

- The submission recommends that product and hemp seed oil exceptions be removed from each of the Schedule 8 entries, that the limits for hemp seed oil and other products of 50 mg/kg or less of tetrahydrocannabinols be reinstated, and that no limits for other cannabinoids should apply.

Delegates' final decision

The delegate has deferred making a final decision at this time regarding the possible rescheduling of cannabis. The deferral of a final decision will allow sufficient time for the delegate to thoroughly consider all public submissions on the interim decision, including two late submissions. Further information on the final decision regarding the possible rescheduling of cannabis is likely to be provided by late May 2017. Should the final decision be released at this time and require an implementation date, it will be announced at the time of publication.

2.4 Epidermal Growth Factor

Referred scheduling proposal

An applicant has proposed to amend the wording of the Schedule 7 entry for Epidermal Growth Factor (EGF), to exempt topical cosmetic preparations containing low concentrations of transgenic plant-made epidermal growth factor from the scope of the Schedule 7 entry.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 7 – Proposed amended Entry

EPIDERMAL GROWTH FACTOR **except**:

a) in preparations for human therapeutic use; or

b) in topical cosmetic preparations containing 0.0002 % or less of transgenic, plant-made epidermal growth factor.

The applicant's reasons for the proposal are:

- The wording of the current Schedule 7 entry for EGF captures any use of EGF other than for human therapeutic use. This is despite the original scheduling submission relating to injectable u-hEGF (urinary human EGF).
- Since the addition of EGF into the SUSMP after the November 1996 advisory committee meeting, there have been significant technological developments in cosmetic product innovation, such as the development of recombinant chemicals in plants for cosmetic use. These substances are commonly used topically in very low concentrations in cosmetic products, having acceptable safety profiles and meeting international regulatory requirements for cosmetic use.
- By amending the Schedule 7 entry, the applicant proposes that this would allow supply of their cosmetic products to Australian consumers within the provisions of Australian consumer protection laws and therefore be able to compete with similar cosmetic products available to purchase online via overseas websites.

Current scheduling status

Epidermal growth factor is in Schedule 7 and Appendix J of the Poisons Standard as follows:

Schedule 7

EPIDERMAL GROWTH FACTOR **except** in preparations for human therapeutic use.

Appendix J

EPIDERMAL GROWTH FACTOR, Condition 1 (Not to be available **except** to authorised or licensed persons).

Relevant scheduling history

In November 1996, the NDPSC considered an application for a recombinant epidermal growth factor for use in sheep. It was listed in the SUSMP in Schedule 7 and Appendix J, Condition 1.

In June 2008, the NDPSC considered a minor editorial amendment to the Schedule 7 entry of epidermal growth factor, changing the entry from "other than for" to "**except** for" in reference to "preparations for human therapeutic use".

Australian and international regulatory information

No information was found on the clinical use of EGF in Australia, the USA or EU. It has been used experimentally to treat diabetic foot ulcers (https://www.ncbi.nlm.nih.gov/pubmed/23396236) and mucositis in patients undergoing radiotherapy (https://www.ncbi.nlm.nih.gov/pubmed/19514089). A collation of published papers (through PubMed and Bioline International) related to the clinical use of EGF was published in 2009 (http://onlinelibrary.wiley.com/doi/10.1111/j.1742-481X.2009.00622.x/full).

Substance summary

Human epidermal growth factor (EGF) is a short 53 amino acid polypeptide. It is secreted by cells and acts as a mitogen, stimulating cellular proliferation, differentiation and survival primarily through the epidermal growth factor receptor (EGFR).

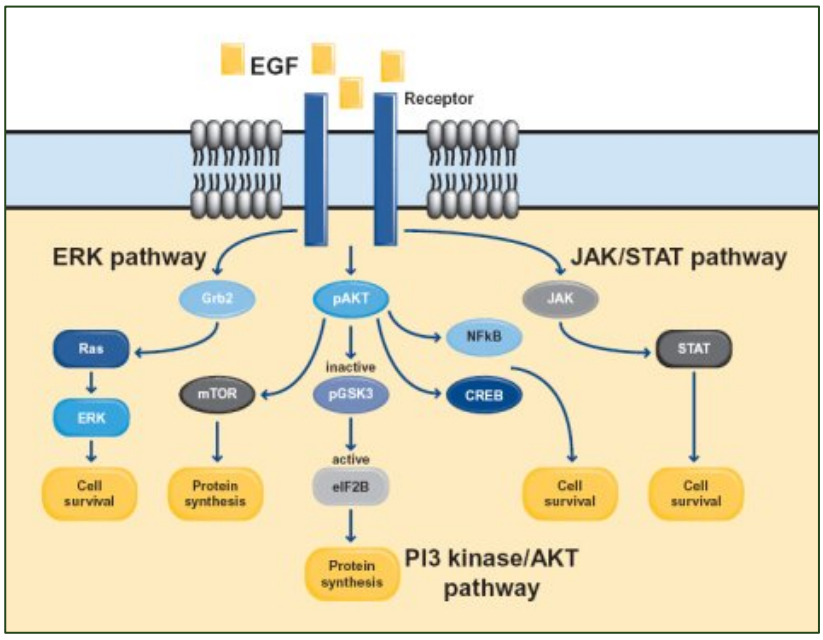


Figure 2.4: Signal transduction activity resulting from EGF binding to its receptor. [28]

The applicant summarises the plant-made EGF as follows:

- Barley sh-Oligopeptide-1 (CAS # 1807528-51-3) is a plant-produced peptide expressed from an in vitro synthesized gene with a barley (*Hordeum vulgare*) codon optimization.
- Barley sh-Oligopeptide-1 is a single chain recombinant human-like growth factor, produced by the barley plant (*Hordeum vulgare*) after insertion of a copy of a human gene into the barley DNA.

[28] Sourced from: http://www.abcam.com/index.html?pageconfig=resource&rid=10723

- Barley sh-Oligopeptide-1 contains 53 amino acids (aa) and an *N*-terminal 6 aa histidine tag for a total length of 59 aa and has a predicted molecular mass of 7 kDa. The starting gene that is inserted into the barley DNA is synthesized *in vitro* to be identical to the sequence of the human gene that codes EGF (rhEGF; NP_001954.2). The synthesized gene is later modified with both (1) codon optimization to adjust the synthesized DNA sequence to the natural barley genomic codon frequency and (2) with histidine-based oligopeptide as His-tag for purification.
- The applicant claims that by using barley as a production host, bypassing the use of bacterial or animal cell systems, the peptide is animal-free and endotoxin-free. Testing by a third party research service organization (Charles River Laboratories, France) confirms that barley produced proteins typically contain more than 200 times lower levels of endotoxins than are allowed in most other commercially available product.[29]

Pre-meeting public submissions

One (1) pre-meeting submission was received which supported the proposal on the basis that it will align Australian regulatory controls with comparable overseas jurisdictions.

Summary of Joint ACCS-ACMS advice to the delegate

The committee advised that the current scheduling of epidermal growth factor remains appropriate.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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; (f) any other matters that the Secretary considers necessary to protect the public health

The reasons for the advice comprised the following:

- Low risk of systemic absorption at low dermal concentration as demonstrated by the limited evidence presented by the applicant does not inform risk/benefit profile sufficiently
- Cosmetic use of peptides and growth factors has increased since original consideration, which was for a broad administration and use of EGF.
- Danger of toxicity minimised by lack of transdermal absorption. Topical product only with no potential for abuse.
- Dependant on concentration in substance, application is for very low concentration.
- Lack of information associated with local toxicological effects.
- There is a lack of data showing safety and no information provided of local effect and concern of therapeutic intent.

Delegates' considerations

The delegates considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACCS-ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)

[29] Magnusdottir A, Vidarsson H, Björnsson JM, and Örvar BL (2013), 'Barley grains for the production of endotoxin-free growth factors', *Trends in Biotechnology*, 31 (10), 572-580.

- Other relevant information.

Delegates' interim decision

The delegates' interim decision is that the current scheduling of epidermal growth factor remains appropriate.

The delegates considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the interim decision are the following:

- The delegates acknowledge and agree with the committee's advice.
- Limited evidence was presented by the applicant to demonstrate that there is a low risk of systemic absorption at low dermal concentrations. Lack of information on potential local toxicity.
- Danger of toxicity minimised by low transdermal absorption. Topical product only with no potential for abuse. However, there is a lack of safety data and no information was provided on local effect.
- Concern around therapeutic intent. Cosmetic use of peptides and growth factors has increased since original EGF scheduling.

Public submissions on the interim decision

Two submissions were received and both opposed the delegate's interim decision. The main points were:

- Plant-made EGF for topical cosmetic use is currently permitted in EU, USA and Canada.
- The scheduling assessment factors for Schedule 7 items are inconsistent with the risk profile of plant-made EGF for topical cosmetic use.
- The contemporary use pattern of low concentration plant-based EGF for topical use is inadvertently captured by the 1996 NDPSC decision on EGF was in relation to a veterinary application of injectable EGF and should be updated accordingly.

Delegates' final decision

The delegates note the submissions and have confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegates' final decision is that the current scheduling for epidermal growth factor remains appropriate.

2.5 Fennel Oil

Referred scheduling proposal

The TGA has proposed that a new Schedule 5 entry be created for fennel oil (active component of fennel oil - methyl chavicol), with consideration of the appropriateness of low volume containers with a restricted flow insert, Medicines Advisory Statements, such as 'keep out of reach of children'; or exemption cut-off of 5 per cent or less of methyl chavicol.

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 5 – New Entry

FENNEL OIL **except**:

a) in medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert and compliant with the requirements of the Medicines Advisory Statements Specification;

b) in preparations other than medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert, and labelled with the warning:

KEEP OUT OF REACH OF CHILDREN; or

c) in preparations containing 5 per cent or less of methyl chavicol.

The applicant's reasons for the request are:

- Fennel oil should be included in Schedule 5 with the same restrictions as basil oil.
- Fennel oil, as with basil oil, may contain methyl chavicol (estragole) (see Substance Summary).
- The reasons are identical to those for basil oil, which was added to Schedule 5 in February 2000 on the basis of the potential for basil oil to contain methyl chavicol (estragole), which has acute oral toxicity in rats and which can be metabolised to a carcinogenic metabolite (1'-hydroxyestragole).
- In March 2016, the CMES of the TGA undertook a safety evaluation of fennel oil to ensure that the ingredient is appropriate for the low-risk listed complementary medicines. The safety evaluation of fennel oil incorporated information from international regulatory agencies, including the National Toxicology Program and academic literature.

Current scheduling status and relevant scheduling history

Fennel oil is not specifically scheduled in the Poisons Standard however basil oil (which also may contain methyl chavicol) is included in Schedule 5 and Appendix E as follows:

Schedule 5

BASIL OIL – **except**:

a) in medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert and compliant with the requirements of the Medicines Advisory Statements Specification;

b) in preparations other than medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert, and labelled with the warning:

KEEP OUT OF REACH OF CHILDREN; or

c) in preparations containing 5 per cent or less of methyl chavicol.

Appendix E, Part 2 – BASIL OIL

Warning statements: A [For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once)], G3 (If swallowed, do NOT induce vomiting).

Basil Oil is also included in Part 2.4 with a container nominal capacity limit of 200 mL or less for CRCs.

Australian and international regulatory information

The ARTG contains multiple entries for listed medicines containing fennel oil. It is currently used as an excipient in 17 listed medicines and as an active in eleven listed medicines.

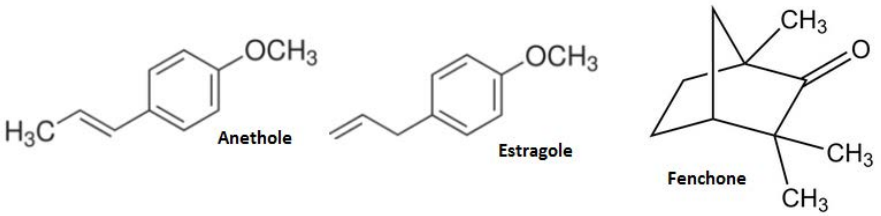
Fennel oil is listed in the Therapeutic Goods (Permissible Ingredients) Determination No. 1 of 2017 as an active, excipient and homoeopathic preparation ingredient. There are no specific requirements applying to the ingredient.

Fennel oil is unclassified in New Zealand and the USA with brief searches for drug products or medicines containing fennel oil, methyl chavicol, chavicol, or estragole on the FDA or Medsafe databases returning no information.

Substance summary

Fennel oil is extracted from the seeds of *Foeniculum vulgare* Mill. (Apiaceae; International Plant Names Index: kew-2813604).

Table 2.5: General information

Property	Fennel oil
CAS No.	8006-84-6.
Australian Approved Name (AAN)	Fennel oil (53603)
Structure of major volatile components of fennel oil	

There are two varieties of fennel in use – sweet fennel (*Foeniculum vulgare* Mill. subsp. *vulgare* var. *dulce* (Mill.) Batt.) and bitter fennel (*Foeniculum vulgare* Mill. subsp. *vulgare* var. *vulgare*). The oils extracted from the two varieties differ slightly in their chemical composition. Sweet and bitter fennel oils contain several components of which *trans*-anethole (50-80%) and estragole (methyl chavicol, 5-20%) are of concern due to their toxic effects.

The safety report concluded that on the basis of the unequivocal evidence of carcinogenicity for estragole, in combination with the current Schedule 5 entry for basil oil (containing a similar content of estragole), suggests that fennel oil should also be scheduled with the similar restrictions.

Pre-meeting public submissions

One (1) public submission was received. The submission did not indicate whether or not it supported the proposal. The main points were:

- Assumes that the intent of the scheduling proposal for fennel oil is to create a new schedule entry for fennel oil in line with the existing schedule entry for basil oil.
- The Schedule 5 proposal has the potential to impact on the use of fennel oil in non-medicinal uses and notes that the consideration of this scheduling proposal by the ACMS and related public notice may not have alerted those that may be impacted by the non-medicinal uses of fennel oil.

Summary of Joint ACCS-ACMS advice to the delegate

The committee advised that a new Schedule 5 entry be created for fennel oil as follows:

Schedule 5 – New entry

FENNEL OIL **except**:

a) in medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert and compliant with the requirements of the Medicines Advisory Statements Specification;

b) in preparations other than medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert, and labelled with the warning:

KEEP OUT OF REACH OF CHILDREN; or

c) in preparations containing 5 per cent or less of methyl chavicol.

Appendix E, Part 2 – New Entry

FENNEL OIL

Standard Statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once).), G3 (If swallowed, do NOT induce vomiting)

2.4 Child resistant closures – New Entry

Column 1
Name of the poison: Fennel oil when included in Schedule 5

Column 2
Nominal capacity: 200 millilitres or less

The ACCS/ACMS advised an implementation date of **1 June 2017**

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the advice comprised the following:

- The substance remains available. It has no therapeutic benefit and is used primarily as a flavouring. There may be valid uses in aroma and flavour areas.
- Acute toxicity and potential carcinogenicity of the component methyl chavicol.
- There is potential for fennel oil containing methyl chavicol to result in human toxicity, as indicated by the acute oral toxicity in the rat and its carcinogenic metabolite.
- The proposed controls will make the chemical available but ensure that accidental overexposure will be significantly reduced.
- Smaller volumes and preparations containing methyl chavicol in concentrations less than 5% pose reduced risk and would be in line with basil oil scheduling.

Delegates' considerations

The delegate considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegates' interim decision

The delegates' interim decision is that a new Schedule 5 entry be created for fennel oil.

The proposed wording for the schedule and appendix entries is as follows:

Schedule 5 – New Entry

FENNEL OIL **except**:

a) in medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert and compliant with the requirements of the Medicines Advisory Statements Specification;

b) in preparations other than medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert, and labelled with the warning:

KEEP OUT OF REACH OF CHILDREN; or

c) in preparations containing 5 per cent or less of methyl chavicol.

Appendix E, Part 2 – New Entry

FENNEL OIL

Standard Statements: A (For advice, contact a Poisons Information Centre (e.g. phone Australia 13 11 26; New Zealand 0800 764 766) or a doctor (at once).), G3 (If swallowed, do NOT induce vomiting)

Part 2, Section 2.4 Child-resistant closures – New Entry

Column 1, Name of the poison: Fennel oil when included in Schedule 5.

Column 2, Nominal capacity: 200 millilitres or less.

The proposed implementation date is **1 June 2017**.

The delegates considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the interim decision are the following:

- The delegates acknowledge and agree with the committee's advice.
- There is potential for fennel oil containing methyl chavicol to result in human toxicity, as indicated by the acute oral toxicity in the rat and its carcinogenic metabolite.

- The proposed controls will make the chemical available but ensure that accidental overexposure will be significantly reduced. The substance remains available. It has no therapeutic benefit and is used primarily as flavouring.
- Smaller volumes and preparations containing methyl chavicol in concentrations less than 5% pose reduced risk and would be in line with basil oil scheduling.

Public submissions on the interim decision

One (1) submission was received, which opposed the delegate's interim decision. The main points were:

- According to IFRA there is a significant difference in concentrations of estragole between basil and fennel oils. The submission questions the appropriateness of scheduling fennel oil with similar restrictions to those for basil oil.

Delegates' final decision

The delegates note the submission and have confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegates' final decision is that a new Schedule 5 entry be created for fennel oil with an implementation date of **1 June 2017**.

3. Advisory Committee on Medicines Scheduling (ACMS #19)

Summary of delegate's final decisions

The final decisions listed below all have an implementation date of **1 June 2017** unless separately specified.

Substance	Final decision
Vitamin D	**Appendix H – New Entry** VITAMIN D
Melatonin	The current scheduling for melatonin remains appropriate.
Paracetamol/caffeine	**Schedule 2 – Amend Entry** PARACETAMOL for therapeutic use: a) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than 12 dosage units per pack; or b) in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or c) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or e) in individually wrapped powders or sachets of granules enclosed

Substance	Final decision
	in a primary pack containing more than 50 wrapped powders or sachets of granules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or f) in other preparations **except**: i) when included in Schedule 3 or 4; or ii) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaifenesin or when combined with effervescent agents) when: (A) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules, (B) compliant with the requirements of the Required Advisory Statements for Medicine Labels, (C) not labelled for the treatment of children 6 years of age or less, and (D) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaifenesin; or iii) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaifenesin or when combined with effervescent agents) when: (A) packed in blister or strip packaging or in a container with a child-resistant closure, (B) in a primary pack containing not more than 20 tablets or capsules, (C) compliant with the requirements of the Required Advisory Statements for Medicine Labels, (D) not labelled for the treatment of children 6 years of age or less, and (E) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaifenesin.
Vardenafil	The current scheduling of vardenafil remains appropriate.

Substance	Final decision
Cetirizine hydrochloride	**Schedule 4 –Amend Entry** CETIRIZINE HYDROCHLORIDE **except**: a) when included in Schedule 2 ; or b) in divided preparations for oral use for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when: i) in a primary pack containing not more than 10 days' supply; and ii) labelled with a recommended daily dose not exceeding 10 mg of cetirizine hydrochloride. **Schedule 2 –Amend Entry** CETIRIZINE HYDROCHLORIDE in preparations for oral use **except** in preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age an over when: a) in a primary pack containing not more than 10 days' supply; and b) labelled with a recommended daily dose not exceeding 10 mg of cetirizine hydrochloride.
Tianeptine	**Schedule 4 – New Entry** TIANEPTINE. **Appendix D Item 5 – New Entry** TIANEPTINE.
Olaparib	**Schedule 4 – New Entry** OLAPARIB.
Ceritinib	**Schedule 4 – New Entry** CERITINIB.
Panobinostat lactate	**Schedule 4 – New Entry** PANOBINOSTAT.
Brivaracetam	**Schedule 4 – New Entry** BRIVARACETAM. **Appendix K – New Entry** BRIVARACETAM

Substance	Final decision
Guanfacine hydrochloride	**Schedule 4 – New Entry** GUANFACINE. **Appendix K – New Entry** GUANFACINE
Follitropin delta	**Schedule 4 – New Entry** #FOLLITROPIN DELTA. **Appendix D, Item 1 – New Entry** FOLLITROPIN DELTA (recombinant human follicle-stimulating hormone) for human use. **Index – New Entry** **FOLLITROPIN DELTA** cross reference: FOLLICLE-STIMULATING HORMONE, RECOMBINANT HUMAN Schedule 4 Appendix D, Item 1

3.1 Vitamin D

Referred scheduling proposal

An application was submitted to include Vitamin D in Appendix H in the Poisons Standard.

Scheduling application

This is a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Appendix H – New Entry

VITAMIN D.

The applicant's reasons for the request are:

- Since August 2015, a high-dose (cholecalciferol 7000 IU (175 micrograms)) vitamin D has been available as a Schedule 3 medicine with a dose of one capsule per week. Adherence to vitamin D supplementation is low and adherence is an important aspect of a therapeutic regimen for osteoporosis. Meta-analysis has demonstrated that weekly dosing doubles the odds of medication adherence compared to daily dosing (low dose vitamin D).
- The uptake of weekly dose products is low and the reason appears to be that most consumers purchase the unscheduled daily dose vitamin D products via the checkout in pharmacies or supermarkets, both well beyond the range of influence of pharmacists. The result is that while pharmacists may be aware of the compliance benefits of once weekly vitamin D, they would only have limited opportunity of discussing this with consumers.
- The ability to advertise the weekly product would prompt consumers to ask the pharmacist about its availability and appropriateness. Increased uptake would improve patient compliance, the ability to coordinate with weekly dose regimes of related medicines (e.g. bisphosphonates) and increased convenience for consumers.

- A position statement commissioned by the Australia and New Zealand Bone and Mineral Society and Osteoporosis Australia reported that an estimated 31% of adults in Australia have inadequate vitamin D status (serum 25-OHD level <50 nmol/L) increasing to more than 50% in women during winter-spring and in people residing in Southern states (Nowson, C.A., et al. Vitamin D and health in adults in Australia and New Zealand: a position statement. Med J Aust, 2012. 196).

- Australian studies have shown that the majority of aged care residents (55-85%) have vitamin D deficiency (Nowson, C.A., et al. Vitamin D in Australia: Issues and recommendations. Australian Family Physician, 2004. 33: p.133-138). Other people at high risk of vitamin D deficiency include people with limited sun exposure (e.g. those with skin conditions where avoidance of sunlight is advised, people who are institutionalised, those with dark skin, particularly if veiled), the obese and patients with malabsorption or on certain medications (e.g. anti-epileptic medications) that increase the excretion of vitamin D.

Current scheduling status

Vitamin D is currently listed in Schedule 3 and Schedule 4 of the SUSMP as follows:

Schedule 4

VITAMIN D for human internal therapeutic use **except**:

a) in preparations containing 25 micrograms or less of vitamin D per recommended daily dose; or

b) when included in Schedule 3.

Schedule 3

VITAMIN D for human therapeutic use in preparations containing 175 micrograms or less of vitamin D per recommended single weekly dose **except** in preparations containing 25 micrograms or less of vitamin D per recommended daily dose.

Vitamin D is cross-referenced with cholecalciferol and ergocalciferol in the Index.

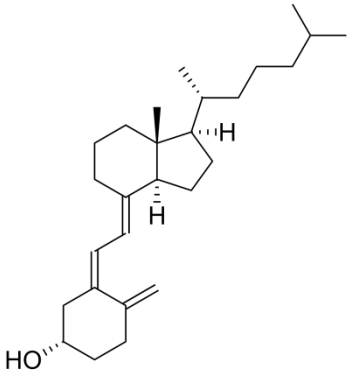
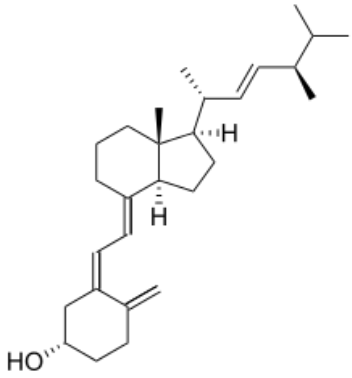
Relevant scheduling history

In October 2012, the ACMS considered a proposal by the same applicant to create a new Schedule 3 entry for vitamin D to allow a weekly dose up to 175 micrograms per recommended dose and to include vitamin D in Appendix H. The ACMS supported the proposal to allow the higher weekly dose, but advised against an Appendix H entry. Some members supported the Appendix H entry, stating that it would promote awareness of the weekly dosage regime. Other members did not support the Appendix H entry as public health activities were considered sufficient to promote appropriate use of vitamin D. There were also concerns about off label use and no limits on pack sizes. The committee also noted that other vitamin D products, as different formulations, were unscheduled and could be advertised. The delegate made a final decision (8 February 2013) to include vitamin D, as a single weekly dose of up to 175 micrograms (7000 IU), in Schedule 3 and not to include vitamin D in Appendix H.

Substance summary

Vitamin D is available primarily as cholecalciferol (vitamin D3), and ergocalciferol (vitamin D2). The major natural source of vitamin D in humans comes from the action of ultraviolet light on 7-dehydrocholesterol in the skin to form provitamin D3 which is then converted to cholecalciferol.

Table 3.1: Chemical information

Property	Cholecalciferol (vitamin D3)	Ergocalciferol (vitamin D2)
CAS No.	67-97-0	50-14-6
Chemical structure		
Molecular formula	$C_{27}H_{44}O$	$C_{28}H_{44}O$
Molecular weight	384.6	396.7
Units	25 micrograms = 1000 IU 175 micrograms =7000 IU	-
AAN	cholecalciferol	ergocalciferol
Chemical name	(5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-trien-3β-ol	(5*Z*,7*E*,22*E*)-9,10-secoergosta-5,7,10(19),22-tetraen-3β-ol

Pre-meeting public submissions

Four (4) public submissions were received and all supported the proposal. The main points were:

- Low vitamin D can be corrected with appropriate supplementation. It commonly takes 2-3 months to restore optimal vitamin D levels. A minimum serum level of 50 nmol/L is recommended at the end of winter or in early spring (when levels are the lowest). Currently most vitamin D supplements are daily tablets with 1000 IU/tablet. The availability of an equivalent weekly dose is additional choice and potential benefit for consumers needing vitamin D supplementation. It can also assist in compliance, particularly for patients requiring supplementation over long periods.
- Toxicity related to vitamin D is generally restricted to large doses, far in excess of the dose available in a weekly tablet (equivalent to 7 daily 1000 IU tablets).
- Presumes that the proposal relates to Schedule 3 Vitamin D, once-a-week products (7000 IU) that currently cannot be advertised, since Vitamin D once daily products (1000 IU) listed as complementary medicines may be advertised. Assumes the usual advertising rules and regulations will apply and that it would not be likely that off-label use could be inadvertently promoted as a consequence of an Appendix H listing.
- The benefits of a simplified dosing schedule, improved adherence to treatment, known safety profile and low toxicity all support appropriate advertising of the high strength products.
- Permitting advertising of high strength Vitamin D supplements would lead to greater awareness of treatment options for a highly prevalent condition.

- There is minimal chance that the product would be inadvertently promoted when safeguards exist such as packaging, pharmacist intervention, and current regulations and advertising approvals.
- The benefits of advertising and raising awareness of Vitamin D to the undiagnosed and untreated community far outweigh any potential risks and are in the public health interest. Low vitamin D levels is a public health issue and relevant to certain groups of the Australian population.
- Potential off-label use leading to adverse clinical outcomes would be minimal as pharmacist intervention and advice is likely to enhance adherence and minimise incorrect dosing. If a consumer did inadvertently take a daily dose of the 175 µg product, the risk of toxicity is minimal. Although there may be a risk that some consumers would initiate self-medication as a result of seeing a branded advertisement, lower dose vitamin D products are already readily available to consumers and any request for the higher dose Schedule 3 product would be handled through pharmacist intervention.
- One of the submissions gave conditional support to the proposal, supporting the proposal on the condition that any advertising highlights a mandatory role of pharmacists in determining suitability for consumers. The main points were:
  - All advertisements must comply with the requirements specific to vitamins, as outlined in the Therapeutic Goods Advertising Code.
  - The inclusion of vitamin D on Appendix H has the potential to increase consumer awareness about vitamin D medicines that may improve medicine adherence and encourage discussions with health professionals.
  - The risk of inappropriate use or over consumption are small and are further reduced through the mandatory oversight of a pharmacist assessing therapeutic need and the labelling on the medicines.

Summary of ACMS advice to the delegate

The Committee recommended that Vitamin D be entered in Appendix H of the Poisons Standard.

The Committee also recommended an implementation date of **1 June 2017**.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the advice comprised the following:

- Access for high-risk consumers to a once-weekly dose of Vitamin D from a pharmacist for effective ongoing supplementation is likely to be beneficial and safe. The compliance benefits, low-risk nature of the product and safeguards inherent in Schedule 3 mean the benefits of advertising the availability of this product exceed any potential risks.
- Some of the risks to an Appendix H entry include: inter-individual tolerance to vitamin D varies considerably and infants and children are more susceptible, according to the approved PI. Inadvertent or deliberate misuse resulting in excessive dosing of vitamin D is also possible. Excessive intake of vitamin D can lead to development of hypercalcaemia and associated effects of hypercalciuria, ectopic calcification, renal and cardiovascular damage. Other symptoms of overdose are listed in the PI and CMI and may include anorexia, lassitude, nausea, vomiting, bone pain, weight loss and other effects.
- Vitamin D is relatively safe and it is difficult to overdose on a Schedule 3 preparation, particularly if given under medical supervision through a pharmacist. The benefits include that some consumers find convenience in the Schedule 3 once-a-week dosage regime. This may lead to improved adherence to supplementation, particularly for long term regular treatment, and may be

beneficial particularly for those with more severe deficiency or at higher risk (e.g. aged care residents, those with limited sun exposure, obese people and those with malabsorption conditions).

- Weekly dose Vitamin D [contains 7000 IU (equiv. to 175 micrograms) cholecalciferol per capsule] is indicated for: (a) treatment of vitamin D deficiency in adults or adolescents as directed by a medical practitioner or pharmacist and (b) prevention of vitamin D deficiency in high risk individuals under the supervision of a medical practitioner or pharmacist.
- Vitamin D has low toxicity, is safe and is very difficult to overdose. The chance of significant toxicity from inclusion in Schedule H is low, particularly as large doses of Vitamin D (50,000-150,000 IU) are given under medical supervision without toxicity issues. In the event that the one-a-week formulation is taken as a daily dose (in error), the potential for toxicity is low. However, there are risks with excessive intake (see above).
- Dosage is as per the Schedule 3 listing [one capsule (7000 IU / 175 micrograms cholecalciferol) per week]. The product is quite well differentiated through labelling/product name and is available in a blister pack containing 30 capsules although this pack size is not limited through scheduling. One pack would last 30 weeks.
- There is little if any potential for abuse. Lower dose Vitamin D products have been available to consumers for many years at the supermarket and other retail outlets yet consumer awareness of the availability of this once-weekly treatment is low due to prohibition of all forms of advertising.
- Appendix H listing improves consumer awareness of access to an effective weekly supplementation treatment via a pharmacist and potential to improve adherence and health outcomes.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that a new Appendix H entry for Vitamin D is appropriate.

The proposed wording for the appendix entry is as follows:

Appendix H — New Entry

VITAMIN D

The proposed implementation date is **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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 the public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Access for high-risk consumers to a once-weekly dose of Vitamin D from a pharmacist for effective ongoing supplementation is likely to be beneficial and safe. The compliance benefits, low-risk nature of the product and safeguards inherent in Schedule 3 mean the benefits of advertising the availability of this product exceed any potential risks.
- Dosage is as per the Schedule 3 listing [one capsule (7000 IU / 175 micrograms cholecalciferol) per week]. The product is quite well differentiated through labelling/product name and is available in a blister pack containing 30 capsules although this pack size is not limited through scheduling. One pack would last 30 weeks.
- There is little if any potential for abuse. Lower dose Vitamin D products have been available to consumers for many years at the supermarket and other retail outlets yet consumer awareness of the availability of this once-weekly product is low due to prohibition of all forms of advertising.
- Appendix H listing improves consumer awareness of access to an effective weekly supplementation via a pharmacist and potential to improve adherence and health outcomes.

Public submissions on the interim decision

No public submissions were received in response to the interim decision for vitamin D.

Delegate's final decision

The delegate has confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegate's final decision is to create a new Appendix H entry for Vitamin D with an implementation date of **1 June 2017**.

3.2 Melatonin

Referred scheduling proposal

An application was submitted to exempt melatonin for human use in preparations containing 1 mg or less of melatonin.

Scheduling application

This was a general application. The Applicant's proposed amendment to the Poisons Standard is as follows:

Schedule 4 – Proposed Amended Entry

MELATONIN for human use **except** when in preparations containing 1 mg or less of melatonin.

The applicant's reasons for the request are:

- Melatonin can currently only be used as an active ingredient for biologicals, export only and prescription medicines and homeopathic formulation in Australia. It is freely sold as a food supplement in USA, Europe and other countries across the globe.
- The applicant provided information that there were products currently being sold in Australia containing melatonin in various strengths and forms. There is also a large market of importation of melatonin via online channels from international retailers, raising concerns that there is a risk to consumers when buying such products from unverified sources some of which are in high dosage strengths of up to 10 mg.
- In general, animal and human studies documented that short-term use of melatonin is safe, even in extreme doses. Only mild adverse effects, such as dizziness, headache, nausea and sleepiness have been reported. No studies have indicated that exogenous melatonin should induce any serious adverse effects. Similarly, randomized clinical studies indicate that long-term melatonin treatment causes only mild adverse effects comparable to placebo.

- Down-scheduling of melatonin will have little or no adverse impact on public health.

Current scheduling status

Melatonin for human use is currently in Schedule 4 of the Poisons Standard.

Relevant scheduling history

In February 1987, the DPSC considered melatonin in a veterinary medicine to synchronise oestrous in ewes. Members agreed to include melatonin in Appendix B.

In February 1997, the NDPSC was advised of the compounding of melatonin capsules by a pharmacist, although the product had not been evaluated or registered by the TGA.

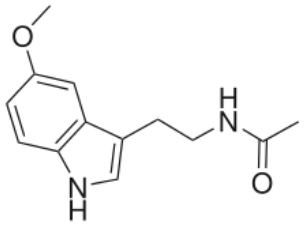
In May 1997, the NDPSC considered responses and information provided following the pre-meeting gazette notice advising it was its intent to consider the scheduling of melatonin at the May 1997 meeting. The NDPSC noted some of melatonin's current popularity related to its benefits in alleviating the symptoms of 'jet lag' and also to claims that it had anti-oxidant, anticancer and anti-aging effects. It was noted that New Zealand had scheduled melatonin as a prescription only medicine, in the absence of adequate data on safety and efficacy being provided to the regulators. The NDPSC considered that insufficient information was available on the safety of melatonin to allow it to remain exempt from scheduling for human therapeutic use and that it should not be available without prescription.

In November 2001, the NDPSC decided that where an entry existed in the Schedules for a particular use/s, no entry should be made in Appendix B; subsequently melatonin was deleted from the Appendix B listing.

Substance summary

Melatonin is a naturally occurring hormone, which is normally produced by the brain's pineal gland. It is involved in co-ordinating the body's sleep cycle by acting on cells in specific areas of the brain and helping to bring about sleep. Blood levels normally increase after the onset of darkness and peak in the middle of the night.

Table 3.2: Chemical information

Property	Melatonin
CAS No.	73-31-4
Chemical structure	
Molecular formula	$C_{13}H_{16}N_2O_2$
Molecular weight	232.3
IUPAC name	*N*-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]; N-[2-(5-methoxyindol-3-yl)ethyl]acetamide
Other chemical name/s	*N*-acetyl-5-methoxy tryptamine
AAN	Melatonin

Pre-meeting public submissions

Seven (7) public submissions were received. Two (2) submissions supported the proposal and five (5) submissions did not support the proposal..

The main points in support were:

- Global relevance of safety as supported by decisions from comparable Regulatory Authorities. Melatonin was reclassified from prescription-only to Natural Health Product (NHP) status under the Health Canada Natural and Non-prescription Health Products Directorate (NNHPD) in 2003. Melatonin has been available for over 20 years in the US dietary supplement market, where it is used by approximately 5% of the population. In 2011 the European Food Safety Authority (EFSA) considered the scientific opinion on the substantiation of a health claim related to melatonin and reduction of sleep onset latency (time taken to fall asleep), which found melatonin to be sufficiently characterised.
- Rescheduling is supported based on the safety profile of melatonin when used as directed on the medicine label and in the context of its proposed indication(s).
- Because of the role of melatonin in sleep and circadian rhythm regulation, and the age related decrease in endogenous melatonin production, melatonin may effectively improve sleep quality particularly in patients who are over 55 with primary insomnia.
- Melatonin seems to be safe when used for up to 6 months and there is some evidence melatonin can be used safely for up to 2 years in some patients.
- Melatonin available without a prescription in Canada and OTC in the USA.
- Helps increase the total sleep time (aspect of sleep quality) in people suffering from sleep restriction or altered sleep schedule, e.g. shift-work and jet lag.
- Melatonin is a safe and effective hormone used to alleviate the symptoms of jetlag. It helps to prevent and/or reduce the effects of jet lag (e.g. daytime fatigue, sleep disturbance) for people travelling by plane easterly across two or more time zones.
- Helps to reduce the time it takes to fall asleep (sleep onset latency aspect of sleep quality) in people with delayed sleep phase disorder.
- Helps re-set the body's sleep-wake cycle (aspect of the circadian rhythm).
- The EFSA recommended 1 mg close to bed time
- Risk mitigation should include:
  - Appropriate health warnings: e.g. consumption with alcohol, other medications or natural health products with sedative properties is not recommended.
  - Directions when taking other medications to consult a health care practitioner prior to use: anticoagulant, anticonvulsant, blood pressure medications, immunosuppressive medications, sedative, hypnotic or psychotropic medications, or steroids.
  - Directions for certain medical conditions, consult a health care practitioner prior to use: asthma, cardiovascular disease, chronic kidney disease, depression, diabetes or hypoglycaemia, hormonal disorder, immune system disease, liver disease, migraine, or seizure disorders.
  - Sleep restriction/altered sleep schedule; delayed sleep phase disorder; sleep-wake cycle: If symptoms persist continuously for more than 4 weeks (chronic insomnia), directions for referral to health care practitioner.
  - Contraindication(s): If you are pregnant or breastfeeding, do not use this product.

  - Known Adverse Reaction(s): Mild gastrointestinal symptoms (nausea, vomiting, or cramping) have been known to occur in which case, discontinue use.
  - Rare allergic reactions have been known to occur in which case, discontinue use.
- Appropriate packaging, dosage, formulation and labelling is necessary.
- Health Canada recommends 3 mg daily for 4 weeks to increase REM sleep in adults.
- Adverse events:
  - There have been 65 reports of mild adverse events, of those 53 where indicated as the single medicine suspected of causing a reaction such as dizziness, nausea and insomnia.
  - Adverse events for Melatonin are low and comparable between Circadin (2 mg) and placebo. There were no treatment-related deaths or serious Adverse Events recorded.
  - Administration of daily doses of up to 300 mg of melatonin without causing clinically significant adverse reactions have been reported in the literature.
- The effects of melatonin on sleep are modest but do not appear to dissipate with continued melatonin use.
- The absolute benefit of melatonin compared to placebo is smaller than other pharmacological treatments for insomnia, however melatonin may have a role in the treatment of insomnia given its relatively benign side-effect profile compared to these agents.
- Lack of side-effects compared to other prescription sleep aids.
- There is no medical requirement for it to remain scheduled due to the lack of any risk at the concentrations proposed.
- It should be removed from the Schedule at concentrations of 5 mg or less. Its removal at concentrations of 1 mg or less as per the application should be considered the bare minimum for action.

The main points in opposition were:

- Creating a scheduling exemption directly from Schedule 4 is inconsistent with Australia's scheduling system and Scheduling Policy Framework.
- While the maximum dosage for melatonin that would be exempt from scheduling under this proposal is half that of the prescription dosage, there is no proposal for limitation on pack sizes.
- There are no restrictions on the number of packs that can be purchased in a single transaction when medicines are sold outside pharmacy.
- Risks in relation to inadvertent excessive or inappropriate intake of melatonin are magnified in non-pharmacy settings with no increased benefit to consumers.
- If products containing melatonin are sold online or in general retail, consumers could purchase these products without any oversight from a health professional to treat what is potentially a serious health condition. It may also encourage patients who are currently under the care of a doctor to abandon their treatment plan as under this scheduling proposal they will not require a prescription for these medicines.
- Lack of clinical evidence regarding use in children.
- The proposal does not define whether the 1 mg referred to is the strength per dose unit or total amount per container (e.g. for a homoeopathic remedy) – assumes the application is based on the New Zealand 1 mg per dose unit application.

- Risks of down-scheduling outweigh the benefits. Potential risk relating to use while pregnant or breastfeeding, and interactions with other substances. Avoidance of the product in pregnancy or women intending to become pregnant; women who are breast-feeding due to lack of direct clinical data; people with auto-immune disorders, and use with fluvoxamine (which can increase bioavailability by 17-fold).

- Long-term toxicity is unknown. Not aware of any recent more comprehensive data on the use of melatonin that would demonstrate or clarify long term safety.

- Misuse potential for inappropriate use, e.g. long-term use in children for sleep conditions more appropriately managed in other ways (e.g. behavioural interventions such as sleep hygiene and stimulus controls) and shift workers, exams, or inappropriate use without first investing in other methods of improving sleep hygiene.

- Increasing patient access to unregistered (dietary supplement melatonin) without healthcare professional oversight could lead to short and long-term health consequences and inappropriate use with considerable safety risks.

- There are risks of underlying conditions not being diagnosed or managed appropriately, of long-term use in certain adults, and in children (for which the safety is unknown), and for dosing with a tablet rather than the first-line behavioural changes recommended to manage insomnia.

- The purposes for which the product would be used are not appropriate for unscheduled supply.

- Melatonin is available as prescription-only in Australia, New Zealand, the United Kingdom and much of Europe. The availability of melatonin in Australia has been determined by the rationale for use based on the role of melatonin in sleep and circadian rhythm regulation and the age-associated decrease in endogenous levels. This is clearly reflected in the parameters of the approved indication of the currently registered melatonin-containing product.

- Melatonin is indicated for primary insomnia, a condition that should be treated and managed by health professionals. Sends wrong message that patients can self-treat insomnia. Insomnia varies in individuals and may be serious underlying condition requiring pharmacist or GP intervention.

- The pharmacokinetic profile of the medicinal product, which has been proven to mimic the endogenous profile, is profoundly different from that of any immediate release preparations. The plasma profile of the melatonin peak following ingestion of 1 mg immediate release preparation is entirely different from the normal endogenous profile of the hormone, leading to an imbalance between the melatonin release and the nocturnal period.

- Efficacy: Only the prolonged release 2 mg melatonin studies have been sufficiently robust to provide appropriate evidence for registration as a medicine. It is not possible to extrapolate the efficacy nor the safety data generated from prolonged release melatonin 2 mg product.

Summary of ACMS advice to the delegate

The Committee recommended that the scheduling of melatonin remains appropriate.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the advice comprised the following:

- The identified risks of changing the scheduling of melatonin mainly involve patterns of use. Such risks included indiscriminate use/misuse by consumers, inadvertent excessive or inappropriate intake of melatonin, potential for underlying sleep conditions not being diagnosed or managed properly (especially in children) and potential for interaction with other drugs (e.g. fluvoxamine, which can increase bioavailability of melatonin by 17-fold). There is also potential that

unscheduled melatonin could be used in children, which also poses a potential for misuse, e.g. for long term treatment or in children with behavioural/discipline issues.

- There are concerns around the current Schedule 4 medicine and the wider indications of its use.
- Melatonin is used to aid sleep or to re-set sleep rhythm. Uses of the existing 2 mg product, registered in 2009, seem to be limited to jet lag and for sleep disorders caused by stress and fatigue.
- Acute use of melatonin appears to have low toxicity. However, chronic use data is lacking. Furthermore, although the frequency and type of adverse effects are not of particular concern, melatonin is a potent hormone and can produce significant effects on multiple body systems at relatively small doses, far less than the cut-off dose proposed. There is no persuasive evidence supplied in the application for the proposed scheduling cut-off dosage.
- The dosage form of the current Schedule 4 medicine is a fast dissolving thin polymer film embedded with melatonin that melts and dissolves in oral cavity saliva. Studies on melatonin have shown no serious adverse events. There is concern about the broader ability of this formulation, in that it may be readily used in children.
- Methods of deterring the increasing volume of personal imports, which are often inappropriate unregistered medicines, should be considered.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that the current scheduling for melatonin remains appropriate.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- The identified risks of changing the scheduling of melatonin mainly involve patterns of use. Such risks included indiscriminate use/misuse by consumers, inadvertent excessive or inappropriate intake of melatonin, potential for underlying sleep conditions not being diagnosed or managed properly (especially in children) and potential for interaction with other drugs (e.g. fluvoxamine, which can increase bioavailability of melatonin by 17-fold). There is also potential that unscheduled melatonin could be used in children, which also poses a potential for misuse, e.g. for long term treatment or in children with behavioural/discipline issues.
- Acute use of melatonin appears to have low toxicity. However, chronic use data is lacking. Furthermore, although the frequency and type of adverse effects are not of particular concern,

melatonin is a potent hormone and can produce significant effects on multiple body systems at relatively small doses, far less than the cut-off dose proposed. There is no persuasive evidence supplied in the application for the proposed scheduling cut-off dosage.

- The dosage form of the current Schedule 4 medicine is a fast dissolving thin polymer film embedded with melatonin that melts and dissolves in oral cavity saliva. Studies on melatonin have shown no serious adverse events. There is concern about the broader ability of this formulation, in that it may be readily used in children.

Public submissions on the interim decision

One (1) public submission was received which opposed the interim decision for melatonin. The submission proposes that the decision not to down-schedule melatonin when used in preparations containing 1 mg or less of melatonin should be re-considered with the following conditions:

- Restrict pack size to 30 dosage units or less.
- Label warning – Not for use in children, pregnant or breast feeding women.
- Label warning – Do not drive or use machinery for 5 hours after taking melatonin.
- Label warning – Consumption with alcohol, other medications or natural health products with sedative properties is not recommended.
- Label warning – Do not take for more than 4 weeks without consulting your healthcare practitioner.
- Label warning – If symptoms persist, please consult your healthcare practitioner.

Delegate's final decision

The delegate has confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegate's final decision is that the current scheduling for melatonin remains appropriate.

Additional reasons for the final decision are the following:

- The significant number of conditions suggested in the submission to control the risk of the medicine if melatonin was to be down scheduled were not specified in the initial application.
- There is no history of use in Australia other than as a Schedule 4 medicine, down scheduling melatonin to general sale is premature.

3.3 Paracetamol compounded with caffeine

Referred scheduling proposal

An application was submitted to amend the scheduling of paracetamol when compounded with caffeine (paracetamol/caffeine), such that it will be exempt from Schedule 2 when supplied in primary packs of not more than 10 tablets/caplets or 5 sachets of powders/granules.

Scheduling application

This is a general application. The Applicant's proposed amendment to the Poisons Standard (which is **not from the current October 2016 Poisons Standard**) is as follows:

Schedule 2 – Proposed amendment

PARACETAMOL for therapeutic use **except**:

a) when included in Schedule 4;

b) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaiphenesin or when combined with effervescent agents) when:

i) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules;

ii) for caffeine only: enclosed in a primary pack that contains not more than 5 such powders or sachets of granules;

iii) compliant with the requirements of the Required Advisory Statements for Medicine Labels;

iv) not labelled for the treatment of children 6 years of age or less; and

v) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaiphenesin; or

c) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaiphenesin or when combined with effervescent agents) when:

i) packed in blister or strip packaging or in a container with a child-resistant closure;

ii) in a primary pack containing not more than 20 tablets or capsules;

iii) for caffeine only: in a primary pack containing not more than 10 tablets or capsules;

iv) compliant with the requirements of the Required Advisory Statements for Medicine Labels;

v) not labelled for the treatment of children 6 years of age or less; and

vi) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaiphenesin.

The applicant's reasons for the request are:

- Paracetamol/caffeine has been available in Australia as a Schedule 2 product since April 2010. The same product has been available in comparable markets (in terms of their population type and regulatory controls) as an unscheduled product for almost 30 years (since 1988 in the UK, 1990 in the USA, 1995 in Ireland and 1999 in Singapore and New Zealand and more recently in 20 other markets).
- The current submission seeks to exempt paracetamol/caffeine from scheduling. Important aspects of this submission are that:
  - The scheduling exemption is only being sought for a small pack size of 10 x paracetamol 500 mg/caffeine 65 mg tablets; and
  - A TGA-approved consumer medicine information (CMI) leaflet will be placed in all packs.
- The ACMS reviewed a scheduling proposal to exempt paracetamol/caffeine in larger pack sizes (not more than 20 tablets/capsules) in November 2014. The decision was to retain the Schedule 2 status. The reasons cited were:
  - Potential risk of harm through excessive unintentional use of caffeine;
  - No strong argument for increasing availability;
  - Concern of the product being used with other caffeine containing products and concern about the toxicity of the combination in intentional overdose;

- Preference for combination analgesics to only be available where professional advice is available;
- There was not a supported argument for public health benefit;
- Risk of consumer confusion without access to advice; and
- Risk of consumer confusion regarding their caffeine intake from multiple sources, given that many caffeine-containing products (including food, drinks and dietary supplements, as well as medicinal products) are freely available to consumers.

There has been little change in the core data sets supporting the favourable clinical efficacy and safety profile of paracetamol/caffeine since the 2014 submission. The current submission therefore focuses primarily on addressing the reasons previously cited by the ACMS to justify retaining paracetamol/caffeine in Schedule 2.

Current scheduling status

Paracetamol is currently listed in Schedule 2, Schedule 3, Schedule 4 and Appendix F in the Poisons Standard. It is also cross-referenced to aspirin, ibuprofen, metoclopramide, salicylamide. The recently implemented scheduling of paracetamol is as follows:

Schedule 4

PARACETAMOL:

a) when combined with aspirin or salicylamide or any derivative of these substances **except** when separately specified in these Schedules;

b) when combined with ibuprofen in a primary pack containing more than 30 dosage units;

c) in slow release tablets or capsules containing more than 665 mg paracetamol;

d) in non-slow release tablets or capsules containing more than 500 mg paracetamol;

e) in individually wrapped powders or sachets of granules each containing more than 1000 mg paracetamol;

f) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules except in Schedule 2;

g) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules **except** when included in Schedule 2;

h) for injection.

Schedule 3

PARACETAMOL when combined with ibuprofen in a primary pack containing 30 dosage units or less **except** when included in Schedule 2.

Schedule 2

PARACETAMOL for therapeutic use:

a) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than 12 dosage units per pack; or

b) in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or

c) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or

e) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

f) in other preparations **except**:

i) when included in Schedule 3 or 4; or

ii) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaifenesin or when combined with effervescent agents) when:

(A) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules,

(B) compliant with the requirements of the Required Advisory Statements for Medicine Labels,

(C) not labelled for the treatment of children 6 years of age or less, and

(D) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaifenesin; or

iii) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaifenesin or when combined with effervescent agents) when:

(A) packed in blister or strip packaging or in a container with a child-resistant closure,

(B) in a primary pack containing not more than 20 tablets or capsules,

(C) compliant with the requirements of the Required Advisory Statements for Medicine Labels,

(D) not labelled for the treatment of children 6 years of age or less, and

(E) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaifenesin.

Appendix F, Part 3 – PARACETAMOL

Standard statements:

97: Adults: Keep to the recommended dose. Don't take this medicine for longer than a few days at a time unless advised to by a doctor.

98: Children and adolescents: Keep to the recommended dose. Do not give this medicine for longer than 48 hours at a time unless advised to by a doctor.

99: If an overdose is taken or suspected, ring the Poisons Information Centre (Australia 13 11 26; New Zealand 0800 764 766) or go to a hospital straight away even if you feel well because of the risk of delayed, serious liver damage.

100: Do not take with other products containing paracetamol, unless advised to do so by a doctor or pharmacist.

Relevant scheduling history

In June 2007, the NDPSC considered the scheduling of paracetamol and caffeine when combined in a compound analgesic as the only active agents. The NDPSC agreed to down schedule paracetamol when combined with caffeine from Schedule 4 as the indications for use, safety profile and potential for misuse met the criteria for a Schedule 2 medicine.

The scheduling of paracetamol combined with caffeine was reviewed in October 2009 by the NDPSC on the grounds of potential toxicity if used in excess. The NDPSC agreed that single active caffeine should remain unscheduled given that the evidence for long-term detrimental or toxic effects from abuse was generally lacking and that the Australian Guidelines for Registration of over-the-counter (OTC) Medicines (ARGOM) required all OTC medicines using caffeine as a stimulant or alerting agent to have an adult dose compliant with "100 mg/dose maximum, which may be repeated at 3-hourly intervals. Do not exceed 600 mg in 24 hours".

NDPSC noted the concern of the addictive nature of caffeine and could lead to dependence and potential overuse or abuse of paracetamol with caffeine preparations possibly resulting in an increase in the likelihood of hepatotoxicity due to the paracetamol. NDPSC noted, however, that they had undertaken extensive deliberations in June 2007 on the scheduling of paracetamol with caffeine. It was asserted that the concerns raised were reviewed comprehensively at that time and the NDPSC had agreed to down-schedule paracetamol with caffeine from Schedule 4 to Schedule 2. NDPSC agreed that applicant had not provided any information about the safety of paracetamol with caffeine that had not been previously considered in June 2007. The Committee decided that Schedule 2 remained appropriate.

In November 2014, the ACMS considered a proposal to amend Schedule 2 entry to exempt paracetamol when compounded with caffeine by the same applicant, in a powder or granule product containing 1000mg or less of paracetamol and in tablets or capsules containing 500mg or less of paracetamol when paracetamol is the only therapeutic active constituent and when supplied in primary packs of not more than 20 tablets/caplets or 10 sachets of powders/granules.

The applicant provided the following reasons to support their 2014 proposal:

- In 2007, the National Drugs and Poisons Schedule Committee (NDPSC) determined that it would be appropriate to consider whether this product (paracetamol compounded with caffeine) could be exempt from scheduling when market experience had been gained with its use as a Schedule 2 product in Australia.
- The paracetamol/caffeine combination analgesic, Panadol Extra®, has been marketed in Australia since April 2010. Substantial in-market experience has been gained with the use of this product as a Schedule 2 medicine for the past four (4) years with no adverse safety signals. Therefore, consideration of exemption from scheduling is considered warranted.

The ACMS advised that the current scheduling of paracetamol when compounded with caffeine remained appropriate.

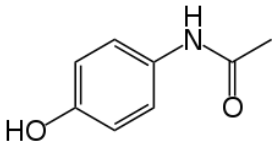
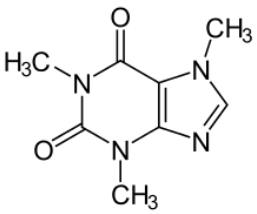
In March 2016, the ACMS considered and supported a proposal by OTC Medicines Evaluation to amend the Schedule 2 entry for paracetamol to (a) restrict the pack size requirements to no more than 100 tablets or capsules per pack and no more than 50 wrapped powders or sachets of granules per pack for domestic supply, and (b) specifically limit bulk pack sizes of paracetamol for supply only to hospital, nursing homes and pharmacies for dispensing purposes. The delegate published a final decision on 23 June 2016 with an implementation date of 1 October 2016.

Substance summary

Paracetamol is a synthetic, non-opiate derivative of *p*-aminophenol that produces analgesia and antipyresis. It is a white crystalline powder with a slightly bitter taste. Paracetamol is soluble in boiling water and freely soluble in ethanol. A saturated aqueous solution has a pH of 5.1 - 6.5 and is stable if stored in an airtight container and is protected from light. The stability of paracetamol decreases in alkaline conditions, where it is slowly broken down into acetic acid and *p*-aminophenol. The pK_a of paracetamol is 9.5.

Caffeine is a methylxanthine that acts on the higher centres of the central nervous system. Its stimulant properties can increase mental alertness and reduce fatigue. Caffeine is not an analgesic, but has been used as an analgesic adjuvant for many years. It is partially soluble in water and ethanol. Caffeine is stable under normal conditions and weakly light sensitive in solution. Caffeine is a white powder or crystals. The pK_a of caffeine is 14.

Table 3.3: Chemical information

Property	paracetamol	caffeine
CAS No.	103-90-2	50-08-2
Chemical name	*N*-(4-hydroxyphenyl)acetamide	1,3,7-trimethylpurine-2,6-dione
AAN	paracetamol	caffeine
Chemical structure		
Molecular formula	$C_8H_9NO_2$	$C_8H_{10}N_4O_2$
Molecular weight	151.2 g/mol	194.2 g/mol
Form	white crystalline powder	white powder or crystals

Pre-meeting public submissions

Six (6) public submissions were received. Two (2) submissions supported the proposal and four (4) submissions did not support the proposal.

The main points in support were:

- This would facilitate greater convenience for consumers.
- Small packs of paracetamol and caffeine preparations are both individually available (in single ingredient preparations) as exempt (unscheduled) products in Australia, and have been for many years.
- Combination paracetamol and caffeine combination products should have been exempt from scheduling from the time of first marketing.
- Support on the basis of harmonisation (with New Zealand, United Kingdom, the USA and Singapore).

- The scheduling of the paracetamol plus caffeine combination products should be consistent with that of single ingredient paracetamol as per the Poisons Standard (in the section titled "Preparations containing poisons listed in two or more schedules"). There appears to be no evidence to suggest that a departure from scheduling policy is warranted for this particular combination product.
- There is a very large patient population that has had experience with the product and the safety profile of the paracetamol and caffeine combination product is very well established. The potential risks are negligible.
- The indications for the paracetamol and caffeine combination product are consistent with those of the single ingredient paracetamol product.
- Consumers are very familiar with appropriate use of paracetamol as an unscheduled product for the temporary relief of pain and discomfort associated with muscular aches and pains, osteoarthritis, headache, toothache, cold & flu symptoms, backache and period pain. There is no evidence that availability of small packs of combination paracetamol and caffeine product for self-selection by consumers will lead to inappropriate use, misuse or excessive use.
- The use of caffeine as an adjuvant to paracetamol is well documented.
- It is well tolerated, has a favourable safety profile and is an efficacious combination offering enhanced analgesic effect.
- There is no evidence of misuse, abuse or inappropriate use.
- Consumers are familiar with managing mild to moderate pain conditions for which this product is indicated. The labelling contains the appropriate warning statements that enable appropriate use of the product.

The main points opposed were:

- Concerned over rise in liver damage due to excessive consumption of products. Research shows that caffeine has little, if any, analgesic effect and would make no real contribution to the analgesic activity of the product. Products containing paracetamol combined with caffeine should be Schedule 4.
- Concerned that a combination product that contains two medicines with well documented adverse effects, in particular hepatotoxicity in paracetamol overuse and that are known to be used inappropriately by consumers, will be made more easily accessible without access to professional advice and counselling by a pharmacist.
- Do not consider that increasing consumer access to paracetamol and caffeine combination products is warranted given the range of analgesic medicines already available outside of pharmacies.
- The potential for consumers to experience an adverse event or outcome is greatly increased if paracetamol and caffeine combination products are made available where professional intervention, and therefore the opportunity to prevent medication misadventure, is not available.
- Consider that the current Schedule 2 classification provides the most appropriate environment for consumers who may require or benefit from supplementary health information or advice, or have the opportunity to have a discussion with the pharmacist.
- Consider it is critical to consider the types of adverse effects that caffeine may cause (e.g. toxicity at >500 mg) when used in combination with other caffeine sources that the consumer may not be aware of.
- Considerable risk of paracetamol toxicity through ingestion of multiple tablets for consumers who rely on the effects of caffeine.

- No factors that have changed since 2014 to warrant a change in scheduling. Reasons for 2014 decision included:
  - Potential risk of harm through excessive unintentional use of caffeine.
  - No strong argument for increasing availability.
  - Concern of the product being used with other caffeine containing products and concern about the toxicity of the combination in intentional overdose.
  - Preference for combination analgesics to only be available where professional advice is available.
  - There was not a supported argument for public health benefit.
  - Risk of consumer confusion without access to advice.
  - Risk of consumer confusion regarding their caffeine intake from multiple sources, given that many caffeine-containing products (including foods, drinks and dietary supplements, as well as medicinal products) are freely available to consumers.
- The risk/benefit profile of this medicine is inconsistent with making it available in general retail, with no access to professional advice.
  - The benefit of taking paracetamol in combination with caffeine is at best marginal and the risks of medication overuse headache are significantly higher compared to paracetamol alone.
  - Caffeine is claimed to enhance the efficacy of paracetamol. However, peak plasma levels and extent of absorption are similar for paracetamol with caffeine and paracetamol alone.
  - Compared with paracetamol alone, a person taking the combination of paracetamol with caffeine may be more likely to experience adverse effects than to get improved analgesia.
  - The extent to which caffeine improves the analgesic effect of paracetamol is uncertain and may not be clinically meaningful.
  - Frequent and prolonged use may result in medication-overuse headache (rebound or withdrawal).
  - Specific risk factor pregnancy and breastfeeding - >200 mg caffeine per day increases risk of miscarriage, >300 mg per day increases risk of preterm delivery and foetal growth retardation.
  - Infants who are breastfed by mothers consuming more than 300 mg caffeine per day may become jittery and restless, and may experience sleep difficulties - If the product is available outside of pharmacies, a mother's caffeine intake (from medicines as well as food and drink) cannot be assessed and discussed; hence they could be at greater risk of inadvertently consuming an excessive amount of caffeine.
  - Products currently registered on the ARTG contain 65 mg of caffeine in each tablet. This means taking just five tablets in a day would exceed the recommended maximum daily limit for pregnant women. This risk is magnified by the fact that single ingredient paracetamol medicines are suitable for use in pregnancy, hence consumers may incorrectly believe the combination medicines are also suitable.
  - While the maximum pack size the applicant is seeking is smaller than the previous proposal, the Guild notes that there are no restrictions on the number of packs that can be purchased in a single transaction when medicines are sold outside of a pharmacy – The risks in relation to the inadvertent excessive or inappropriate intake of caffeine are magnified in non-pharmacy settings with no increased benefit to consumers.
- Concerned that many consumers will make the assumption that paracetamol in combination with caffeine is a 'better' or 'more powerful' medicine than regular paracetamol. If sold in general retail with no professional advice available, consumers may self-select paracetamol in combination with

caffeine, not actually being aware of the potential additional side effects and risks of using this combination product as opposed to regular paracetamol.

Summary of ACMS advice to the delegate

The Committee recommended that the existing Schedule 2 entry be amended for paracetamol when compounded with caffeine as follows:

Schedule 2 – Amend Entry

PARACETAMOL for therapeutic use:

a) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than 12 dosage units per pack; or

b) in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or

c) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or

e) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

f) in other preparations **except**:

  i) when included in Schedule 3 or 4; or

  ii) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaifenesin or when combined with effervescent agents) when:

    (A) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules,

    (B) compliant with the requirements of the Required Advisory Statements for Medicine Labels,

    (C) not labelled for the treatment of children 6 years of age or less, and

    (D) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaifenesin; or

  iii) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaifenesin or when combined with effervescent agents) when:

    (A) packed in blister or strip packaging or in a container with a child-resistant closure,

    (B) in a primary pack containing not more than 20 tablets or capsules,

    (C) compliant with the requirements of the Required Advisory Statements for Medicine Labels,

    (D) not labelled for the treatment of children 6 years of age or less, and

(E) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaifenesin.

The ACMS advised an implementation date of **1 June 2017.**

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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.

The reasons for the advice comprised the following:

- The benefits outweigh the risks.
  - Benefits of "exempt from schedule" availability include consumer convenience and self-care choices, evidence of a small incremental analgesic effect compared to single ingredient paracetamol (although whether this is clinically relevant is unknown), and evidence of faster onset of analgesia with smaller pack size to mitigate risk. Consumers are very familiar with purchase of small pack sizes of analgesics in the open sale environment. Other benefits include the availability of an alternative product where paracetamol alone is not sufficiently effective and when an unscheduled NSAID is not suitable, the prompt availability in supermarkets/convenience outlets as well as an increase in awareness of alternative pain management options.
  - Risks include possible increased risk of harm through excess unintentional use (i.e. accidental overdose), concomitant use with other paracetamol-containing products or foods/beverages/other medicines that contain caffeine and the risk of harm through intentional overdose or misuse, possibility of increased use leading to medication overuse headache.
- The purpose is for temporary relief of pain and discomfort associated with headache, tension headache, migraine, osteoarthritis/arthritis, cold & flu symptoms, toothache, muscular ache, backache, sore throat and period pain. The extent of use of paracetamol 500 mg/caffeine 65 mg in tablet combinations is comparable to that of single ingredient paracetamol. Dosage is 2 tablets every 4–6 hours as needed with a maximum of 8 tablets in 24 hours. It is not recommended for children under 12 years. The length of treatment is indicated for only a few days (as per TGA labelling requirements).
- Labelling and consumer medicine information is as per application. RASML warning statements for paracetamol are on the labelling and additional warning for caffeine is present on the XXX label. The presentation is a small pack size of 10 tablets of paracetamol 500 mg /caffeine 65 mg. A CMI is included with each pack that advises consumers to consult a doctor or pharmacist about using this medicine if they are pregnant, plan to be, or are breastfeeding. Caution is advised in relation to additional tea/coffee intake. External pack labelled with advice when not to use this product and when to check with doctor before use (e.g. if breastfeeding).
- The toxicity of paracetamol is well documented. Potential toxicity occurs with dose of >200 mg/kg (or 10 g) acute ingestion over a 24 hour period. Toxicity can also occur with supratherapeutic doses ingested over a few days. Acute overdose of caffeine can occur with high doses. This is estimated to be 5–10 g (equivalent to 77–154 tablets). Paracetamol at high doses can cause hepatotoxicity.
- Caffeine at high doses may produce headache, tremor, nervousness and irritability and tachycardia; doses of 500–600 mg caffeine per day can cause symptoms such as insomnia, restlessness, and tachycardia. The full dose (8 tablets/day), without concomitant food/drink intake, will reach the recommended daily limit. Beyond this limit, people may start to experience symptoms. This is consistent with labelling advice on sleeplessness.
- There is documented low abuse potential, although regular intake of caffeine can produce tolerance; compulsive drug-seeking behaviour involving caffeine has not been observed. There is

global safety data from over 90 countries, with comparable regulatory systems, where regulatory status of the availability of caffeine/paracetamol combinations is un-scheduled/exempt.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that the existing Schedule 2 entry for paracetamol be amended to include combinations with caffeine.

The proposed schedule wording is as follows:

Schedule 2 – Amend Entry

PARACETAMOL for therapeutic use:

a) when combined with ibuprofen in preparations for oral use when labelled with a recommended daily dose of 1200 mg or less of ibuprofen in divided doses in a primary pack containing no more than 12 dosage units per pack; or

b) in tablets or capsules enclosed in a primary pack containing not more than 100 tablets or capsules; or

c) in tablets or capsules enclosed in a primary pack containing more than 100 tablets or capsules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

d) in individually wrapped powders or sachets of granules enclosed in a primary pack containing not more than 50 wrapped powders or sachets of granules; or

e) in individually wrapped powders or sachets of granules enclosed in a primary pack containing more than 50 wrapped powders or sachets of granules intended only as a bulk medicine pack and labelled 'For dispensing only' and 'This pack is not to be supplied to a patient'; or

f) in other preparations **except**:

i) when included in Schedule 3 or 4; or

ii) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaifenesin or when combined with effervescent agents) when:

(A) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules,

(B) compliant with the requirements of the Required Advisory Statements for Medicine Labels,

(C) not labelled for the treatment of children 6 years of age or less, and

(D) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaifenesin; or

iii) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than caffeine, phenylephrine and/or guaifenesin or when combined with effervescent agents) when:

(A) packed in blister or strip packaging or in a container with a child-resistant closure,

(B) in a primary pack containing not more than 20 tablets or capsules,

(C) compliant with the requirements of the Required Advisory Statements for Medicine Labels,

(D) not labelled for the treatment of children 6 years of age or less, and

(E) not labelled for the treatment of children under 12 years of age when combined with caffeine, phenylephrine and/or guaifenesin.

The proposed implementation date is **1 June 2017**.

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

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- As outlined in the committee's advice the benefits outweigh the risks.
- There is documented low abuse potential, although regular intake of caffeine can produce tolerance; compulsive drug-seeking behaviour involving caffeine has not been observed. There is global safety data from over 90 countries, with comparable regulatory systems, where regulatory status of the availability of caffeine/paracetamol combinations is un-scheduled/exempt.

Public submissions on the interim decision

One (1) public submission was received which supported the interim decision and the reasons for the decision.

Delegate's final decision

The delegate has confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegate's final decision is that the existing Schedule 2 entry for paracetamol be amended to include combinations with caffeine. The implementation date is **1 June 2017**.

3.4 Vardenafil

Referred scheduling proposal

An application was submitted to reschedule vardenafil in oral preparations containing up to 10 mg in Schedule 3.

Scheduling application

This was a general application. The Applicant's proposed amendment to the Poisons Standard is as follows:

Schedule 4 – Proposed Amended Entry

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

Schedule 3 – Proposed New Entry

VARDENAFIL in oral preparations containing 10 mg or less of vardenafil per dosage unit in packs containing not more than 8 dosage units.

The applicant's reasons for the request are:

- To improve access to an effective treatment of verified pharmaceutical quality for an appropriate cohort of adult males suffering from erectile dysfunction (ED), who may not have otherwise consulted a doctor regarding their ED symptoms;
- ED affects at least 20% of Australian men >40 years, with the odds of ED increasing up to 10 times in >70 year-olds. However, the reported prevalence of ED is likely to represent an underestimate because of the general reluctance of men to seek medical advice, the social implication of admitting the condition, and the embarrassment their discussion will cause.
- Improved management of ED may have a potential for public benefit beyond men's sexual health.
- Although ED is rarely the first sign of other emerging medical conditions, it has been correlated with other health conditions; thus opportunities to encourage men reticent to consult a health professional about ED are valuable.
- Of particular concern is the variety of internet-sourced, unapproved ED products that may pose safety risks due to unevaluated ingredients, containing undeclared PDE5 inhibitors or other substances, or are falsely manufactured, packed or advertised counterfeit versions. The scale of the risk these products pose to Australia men appears to be significant (25% of all 2015 TGA safety alerts) and is expected to increase based on 2016 TGA safety alerts to date.
- For ED sufferers who are aware of treatment options, are comfortable enough to discuss their symptoms with a HCP and can afford adequate healthcare, the General Practitioner (GP) is another access option to treatment. However, as men commonly delay or avoid consulting their GP generally and in particular regarding ED, safe, alternative options to access effective treatments such as PDE5 inhibitors appear warranted.
- Vardenafil has a well-characterised and favourable benefit-risk profile. The safety of vardenafil has been well established through clinical trials in more than 52,000 subjects and post-marketing experience since 2003 (up to 107 countries as of 2016) from more than 2.2 Mio patient-years.
- Rescheduling vardenafil up to 10 mg in distinctively labelled packs of up to 8 dosage units as Schedule 3 medicines, when supplied by trained and accredited pharmacists according to a strict screening protocol will provide better access to effective treatment for men with ED and a low risk CV status. More broadly, the proposed treatment algorithm could be seen as patient screening programme focused on CV risk indicators that can identify at-risk patients earlier and thus improve health management and well-being for Australian men.

Current scheduling status

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

Schedule 4

VARDENAFIL.

Relevant scheduling history

In June 2003, the NDPSC considered a proposal to schedule vardenafil as a new medicine. The committee decided to list vardenafil in Schedule 4 on the grounds that the condition being treated necessitated appropriate medical diagnosis and the use of this medicine required patient management and monitoring by a medical professional.

Australian regulatory information

In Australia, vardenafil 5, 10, and 20 mg tablets and vardenafil 10 mg dispersible tablets were registered as Prescription Only Medicines on the ARTG in April 2003.

International regulatory information

Internationally (Canada and USA), vardenafil appears to be classified as prescription medicine.

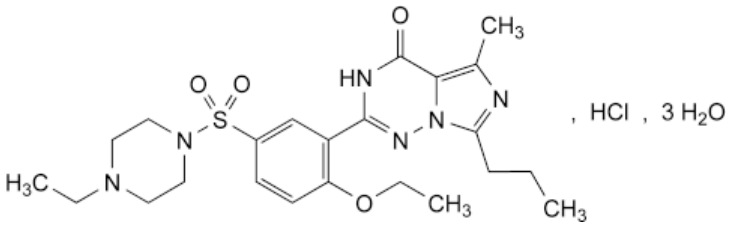
Substance summary

Vardenafil is present in oral dosage forms as vardenafil hydrochloride trihydrate, which is nearly colourless, very slightly soluble in water, soluble in dilute hydrochloric acid and soluble in ethanol.

Vardenafil inhibits the most prominent phosphodiesterase (PDE) in the corpus cavernosum, the enzyme phosphodiesterase type 5 (PDE5), which specifically hydrolyses cGMP. By preventing the breakdown of cGMP, vardenafil allows the male to reach and maintain an erection when sexually stimulated to produce nitric oxide.

The maximum recommended dose is one orodispersible tablet daily (10 mg vardenafil) - Australian Public Assessment Report for Vardenafil (https://www.tga.gov.au/auspar/auspar-vardenafil).

Table 3.4: Chemical information

Property	Vardenafil
CAS No.	330808-88-3 (hydrochloride trihydrate), 224785-91-5 (anhydrous)
Chemical structure	 , HCl , 3 H_2O
Chemical name	2-[2-Ethoxy-5-[(4-ethylpiperazin-1-yl)sulfonyl]phenyl]-5-methyl-7-propylimidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one hydrochloride.
AAN	Vardenafil hydrochloride trihydrate (INNM) and vardenafil (INN)
Molecular formula	$C_{23}H_{32}N_6O_4S{\cdot}HCl{\cdot}3H_2O$ (hydrochloride trihydrate)
Molecular weight	579.1 g/mol (hydrochloride trihydrate)

Pre-meeting public submissions

Seven (7) public submissions were received. Six (6) submissions supported the proposal and one (1) opposed the proposal.

The main points in support were:

- Erectile dysfunction is closely correlated with a number of chronic conditions involving compromised vascular function, such as coronary artery disease, hypertension, diabetes, and hypercholesterolemia. As men with erectile dysfunction are likely to have or to develop cardiovascular risk factors it is important that they seek assistance from a health care professional

at the earliest opportunity. In many cases erectile dysfunction is an early sign of cardiovascular risk development and is a potential indicator for adverse cardiovascular events. Therefore enabling a discussion between men with erectile dysfunction and trained health professionals will go some way to help address the health concern of male cardiovascular risk.

- There are several classes of prescription drugs contribute to sexual dysfunction in men. These include antihypertensives, antidepressants and antipsychotics. Patients who develop drug-induced sexual dysfunction are more likely to be non-adherent to their medicine regimens. Therefore pharmacists have an important role to play in screening and risk assessment of patients who may be suffering from sexual dysfunction caused by a medical condition or the use of a medicine.

- As males traditionally do not engage to the same extent as females with medical practitioners, Pharmacist Only vardenafil represents an opportunity for men who would otherwise not seek primary care support to be assessed by a pharmacist and appropriately referred to a medical practitioner for assessment of their health conditions/comorbidities.

- Availability of Pharmacist Only vardenafil provides an avenue for men to access proven, registered treatments for erectile dysfunction and have related health conditions initially screened by a pharmacist and appropriately referred. An overseas study showed pharmacists can accurately use screening tools to identify erectile dysfunction in their practice.

- Men without a GP will welcome the opportunity to access information and pharmacist screening services for erectile dysfunction.

- Many men suffer in silence and are reluctant to get professional help for their sexual concerns and often do not continue treatment. Men turn to online unregistered and unsafe options for erectile dysfunction which may pose significant safety risks. Many men, in the absence of an easily accessible face-to-face pharmacy erectile dysfunction service, access internet-sourced unregistered erectile dysfunction options. These unregistered erectile dysfunction options have been found to contain undisclosed Schedule 4 medicines with the potential for causing adverse drug reactions and drug interactions if not provided with counselling from a health professional. Increased primary care intervention (by pharmacists) including erectile dysfunction assessment and referral of men who may otherwise choose unregistered medicines via the internet appears significant. Rescheduling vardenafil to an Schedule 3 medicine would reduce the likelihood that men will resort to internet-sourced unregistered options, which are fraught with counterfeiting and variable quality assurance standards, thereby improving safety.

- Vardenafil is generally well tolerated has a well-established safety profile. The risk profile and potential for side effects of the proposed Schedule 3 entry (vardenafil 10 mg – 8 dosage units) is low.

- Several professional bodies indicated that pharmacist training is needed, as this is a new area of practice and there are no similar medications in Schedule 3. Relevant stakeholders need to ensure rigorous, consistent and user-friendly professional education and practice support tools can be developed for the pharmacy profession. Symptoms of erectile dysfunction can be identified by patients and managed by appropriately trained pharmacists with referral to a GP where necessary. Some pharmaceutical professional bodies have developed protocols and training for pharmacists to use to screen/risk assess patients who self-report the symptoms of erectile dysfunction. The protocol was developed in consultation with a range of expert health professionals including urologists, cardiologist and pharmacists, to ensure only low risk patients are supplied vardenafil and all patients with risk factors are referred. A similar scheduling arrangement to that proposed already exists in New Zealand (albeit with sildenafil) and the results there have been positive.

- The proposed Schedule 3 dosage strength of 10 mg and small pack size would limit potential for overdose.

- Researchers at Cancer Council NSW have estimated that by 2017 there will be 200,000 Australian men living post diagnosis and treatment for prostate cancer. Of those who have been treated by the main treatment modalities (radical prostatectomy, radiotherapy and androgen deprivation therapy), some 70% will experience persistent erectile dysfunction. Rescheduling vardenafil to an

Schedule 3 medicine would greatly benefit men suffering from erectile dysfunction following treatment for prostate cancer. It would improve access to an effective registered treatment in a self-care controlled environment, thereby increasing the number of men who seek professional help for their sexual concerns.

- Vardenafil has undergone a full evaluation on registration in Australia no new information that may alter the clinical safety and efficacy profile of this medicine is known.
- The key considerations around whether this rescheduling proposal is acceptable to health professionals and safe for consumers will depend heavily on implementation issues e.g.
  - Screening needed by pharmacists on appropriateness of medicine for consumer
  - Clear criteria for when immediate (or conditional) referral to a medical practitioner is warranted and for these to be clearly highlighted for pharmacists
  - Appropriate communication with prescribers (e.g. consumer's GP, other prescribers in the area)
- A change to Schedule 3 would encourage more men to discuss erectile dysfunction by increasing the availability of treatment options. Pharmacists can play in assessing and providing this medication in a responsible manner, improve accessibility, giving professional advice and support from healthcare professionals.
- Several health risks were identified: risk of arrhythmia; use in patients with hepatic impairment; use in older patients; and potential interaction with other medications. Several professional bodies suggested managing the risks by: additional pharmacist training, use of questionnaires, and limitations on the dosage and maximum pack size allowable in Schedule 3, as proposed by the applicant.
- An appropriate questionnaire and pharmacist training should be mandated as part of any considerations to create a Schedule 3 listing for vardenafil. Mandating or recommending requirements would ultimately be a matter for the States and Territories and the Pharmacy Board of Australia.
- In New Zealand sildenafil (a vardenafil analogue) has been available without a prescription from pharmacists that have completed training endorsed by the Pharmaceutical Society of New Zealand. Arguments presented in New Zealand were:
  - men rarely make an appointment to see the doctor about erectile dysfunction as they often think the problem is too trivial from a medical point of view.
  - it is possible for pharmacists to be trained to screen for, and deal with erectile dysfunction that has a purely psychological origin.
  - the proposed substantial cardiovascular risk screening to be performed by pharmacists would mean that patients could receive not only timely access to sildenafil, but also early cardiovascular disease detection.
  - the improved convenience of obtaining sildenafil from a pharmacist would reduce the number of men attempting to import the medicine from overseas via the internet. In Australia, the TGA regularly publishes safety advisories on products that can be bought from overseas websites that have been registered on the Australian Register of Therapeutic Goods (ARTG). These products often contain undeclared active ingredients such as sildenafil and have not been tested for safety, quality and efficacy.

The main points opposed was:

- If a new Schedule 3 entry is created for vardenafil, the inclusion of vardenafil in Appendix H at this time was not supported given the lack of experience as a Schedule 3 medicine.

- Vardenafil can prolong cardiology QT intervals and increase the risk of arrhythmias, and its use is also cautioned in the setting of hepatic impairment. Community pharmacies do not have adequate resources to screen for these risks.

Summary of ACMS advice to the delegate

The Committee advised that the current scheduling of vardenafil remains appropriate.

The Committee recommended adding this issue to the SPF review – Schedule 3/Schedule 4 boundary for 'switch' products. The Committee also recommended providing feedback to the applicant.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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; (e) the potential for abuse of a substance; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the advice comprised the following:

- Erectile dysfunction can be a marker of an underlying cardiovascular disease, diabetes or endocrine disorder and men should be assessed by a medical practitioner prior to (or at the very least concurrent with) initiation of PDE5 inhibitor treatment. Although vardenafil shows good toxicological profile and is well-tolerated, the cause/aetiology of the medical condition is of greater concern and should first be assessed by a medical practitioner.
- PDE5 inhibitors are commonly misused, often in combination with other drugs such as MDMA (ecstasy/methamphetamines). The rescheduling of vardenafil would most likely not reduce internet purchasing and access to overseas supply of vardenafil.
- The application was predicated on the both pharmacist training and a supply protocol. However, additional pharmacist training and use of a specific supply protocol cannot be mandated for the supply of pharmacist-only Schedule 3 medicines.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that the current scheduling of vardenafil remains appropriate.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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; (e) the potential for abuse of a substance; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Although vardenafil has a good toxicological profile and is well-tolerated, the aetiology of the medical condition should first be assessed by a medical practitioner. Erectile dysfunction can be a marker of an underlying cardiovascular disease, diabetes or endocrine disorder.

- PDE5 inhibitors are commonly misused, often in combination with other drugs such as MDMA (ecstasy/methamphetamines). The rescheduling of vardenafil would most likely not reduce internet purchasing and access to overseas supply of vardenafil.

- The application was predicated on the both pharmacist training and a supply protocol. However, additional pharmacist training and use of a specific supply protocol cannot be mandated for the supply of pharmacist-only Schedule 3 medicines.

Public submissions on the interim decision

Two (2) public submissions were received that opposed the interim decision. The main points were:

- Schedule 3 availability of vardenafil has led to an increase in discussions between men and their healthcare providers in New Zealand. This could be mirrored in Australia if vardenafil is changed to Schedule 3.

- The submission suggests that the rescheduling of vardenafil and the availability of safe, high quality and regulated products may reduce internet purchases of unsafe products. Risk mitigation of illicit use of vardenafil proposed by the submission include, recording vardenafil sales, label warnings, limited Schedule 3 pack sizes and specific counselling against misuse in combination with recreational illicit drugs.

- Pharmacists are involved in Schedule 3 transactions and are able to recommend appropriate products tailored to each specific patient's circumstance. This protocol makes mandating '*additional pharmacist training and use of a specific supply protocol… for the supply of pharmacist-only Schedule 3 medicines'* unnecessary.

- The TGA's existing authority could be utilised in order to mandate risk mitigation activities (E.g. Risk Management Plans (RMPs)) as a condition for approval for Schedule 3 medicines, thus overcoming the delegate's concerns regarding pharmacist practices and training. The submission asserts that existing tools are available to support pharmacist recommendations for medical referral, such as the Pharmacy Society of Australia's (PSA's) clinical intervention standard template 'referral letter' from dispensing software.

- Schedule 3 supply of vardenafil could be provided only to patients who, on pharmacist screening, do not have medication contraindications, medical conditions (or family histories of medical conditions) such as cardiovascular (CV) disease, diabetes or endocrine disorders. Such interactions with a pharmacist will prompt men to consider engaging with a medical practitioner to investigate potential cause of their erectile dysfunction (ED) in addition to providing a new opportunity for blood pressure (BP) checks, other elements of CV screening and pharmacist counselling that otherwise would not have occurred. This protocol is in alignment with existing pharmacy frameworks to provide continued professional training, best pharmacy practices for supply of any new and all existing Schedule 3 medicines, and the PSA's standard for the provision of Schedule 3 medicines as follows:

  – Determine if the patient's symptoms are caused by other conditions and/or

  – Refer the patient to the doctor where required, in accordance with any pharmacy protocol for the medicine in question.

- Current consumer, pharmacist and broader healthcare network attitudes and behaviours in relation to ED have the potential to be impacted by the Schedule 3 availability of vardenafil and the consequential promotional and educational investment in ED medicines.

Delegate's final decision

The delegate has confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegate's final decision is that the current scheduling of vardenafil remains appropriate.

Reasons for the final decision additional to those provided from the interim decision include:

- As there are currently no risk management plans for Schedule 3 medicines it is premature to down-schedule vardenafil where there are no mandated requirements to minimise the risk relating to underlying medical conditions. The delegate will raise this suggestion with the appropriate TGA area as robust RMPs might assist in assessing down-scheduling applications.
- The delegate also notes that no other PDE5 inhibitors have been down-scheduled.

3.5 Cetirizine hydrochloride

Referred scheduling proposal

An application was submitted to reschedule cetirizine hydrochloride from Schedule 2 to unscheduled when in preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over, when in a maximum pack size of 10 days' supply labelled with a recommended daily dose not exceeding 10 mg of cetirizine hydrochloride.

Scheduling application

This was a general application. The applicant's proposed amendment to the Poisons Standard is as follows:

Schedule 4 – Proposed Amended Entry

CETIRIZINE HYDROCHLORIDE **except**:

c) when included in Schedule 2 ; or

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

iii) in a primary pack containing not more than ~~5~~ 10 days' supply; and

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

Schedule 2 – Proposed Amended Entry

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

a) in a primary pack containing not more than ~~5~~ 10 days' supply; and

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

The applicant's reasons for the request are:

- The current proposal aligns with the recent approval for 10 mg loratadine, which is the same class of medicine as cetirizine hydrochloride and is well documented to have a very similar efficacy and safety profile to cetirizine hydrochloride, including sedation potential. This was recognised by the NDPSC in the October 2005 meeting whereby they acknowledged that both loratadine and cetirizine hydrochloride have similar CNS effects which are dose related.

Current scheduling status

Cetirizine hydrochloride is currently in Schedules 4 and 2 of the Poisons Standard as follows:

Schedule 4

CETIRIZINE HYDROCHLORIDE **except**:

a) when included in Schedule 2 ; or

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

i) in a primary pack containing not more than 5 days' supply; and

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

Schedule 2

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

a) in a primary pack containing not more than 5 days' supply; and

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

The scheduling of other histamine H_1-receptor antagonists, loratadine and fexofenadine are as follows:

Loratadine

Schedule 4

LORATADINE **except**:

a) when included in Schedule 2; or

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

i) in a primary pack containing 10 dosage units or less; and

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

Schedule 2

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

a) in a primary pack containing 10 dosage units or less; and

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

Fexofenadine

Schedule 4

FEXOFENADINE **except**:

a) when included in Schedule 2; or

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

i) in a primary pack containing 10 dosage units or less and not more than 5 days' supply; and

ii) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine.

Schedule 2

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

a) in a primary pack containing 10 dosage units or less and not more than 5 days' supply; and

b) labelled with a recommended daily dose not exceeding 120 mg of fexofenadine.

Relevant scheduling history

Cetirizine

In May 1993, the DPSSC decided to include cetirizine hydrochloride in Schedule 4 and Appendix K.

In May 1997, the NDPSC decided to include cetirizine hydrochloride in Schedule 3 as the only therapeutically active substance in divided preparations for oral use containing 10 mg or less of cetirizine hydrochloride. A limit on pack size was not considered necessary. Cetirizine hydrochloride remained in Schedule 4 except when included in Schedule 3.

In February 1998, the NDPSC decided to amend the Schedule 3 entry for cetirizine hydrochloride to include all oral formulations of cetirizine hydrochloride, when it was the only active substance in the preparation (the Schedule 3 entry was no longer to be restricted to divided preparations and the maximum dosage unit size was deleted).

At the February 1999 Meeting, the NDPSC supported a recommendation from the Trans-Tasman Harmonisation Working Party (TTHWP) that, on grounds of harmonisation, cetirizine hydrochloride in preparations for oral use be rescheduled from Schedule 3 to Schedule 2. A consequence of the deletion from Schedule 3 was the deletion of the Appendix H entry.

In November 1999, the NDPSC decided to reschedule cetirizine in all preparations for oral use to Schedule 2. The Appendix H entry for cetirizine was deleted.

In October 2005, the NDPSC considered an application to amend the working of Appendix F Part 1 for cetirizine and to remove cetirizine from oral use from Appendix K. The evidence at the time indicated that cetirizine was no more sedating than loratadine and the NDPSC agreed to alter the wording of Appendix F Part 3 and remove cetirizine for oral use from Appendix K of the SUSDP.

In June 2012, the ACMS advised that cetirizine should be exempt from scheduling, when in divided forms for oral use containing 10 mg or less of cetirizine per dose, in packs containing not more than 5 days' supply for the treatment of seasonal allergic rhinitis.

Loratadine

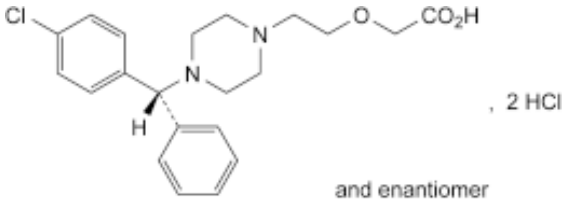
In July 2013, the ACMS considered a proposal to reschedule loratadine from Schedule 2 to unscheduled in oral preparations containing 10 mg or less in packs containing not more than 5 daily doses for the treatment of seasonal allergic rhinitis in adults and children 6 years of age and over, with a warning label recommending a daily dose not exceeding 10 mg loratadine for adults and children with body weight over 30 kg, or recommended daily dose not exceeding 5 mg loratadine for children with body weight 30 kg and under. The ACMS recommended that the current scheduling of loratadine remained appropriate, due to the risk of inappropriate use and delay in correct diagnosis, the lack of data on adverse effects/experiences/poisoning in Australia, no substantial public health benefit in exempting from schedules and a complicated dosage regimen with risk of inappropriate dosing.

In March 2016, the ACMS considered a proposal to increase the pack size of unscheduled loratadine (10 mg or less) divided oral preparations from 5 dosage units to 10 dosage units when used in adults and children 12 years of age and over for the treatment of seasonal allergic rhinitis. The delegate made a final decision (23 June 2016) that the Schedule 2 and Schedule 4 entries for loratadine be amended to increase the unscheduled loratadine dosage from 5 dosage units to 10 dosage units in divided oral preparations when used in adults and children 12 years of age and over for the treatment of seasonal allergic rhinitis with an implementation date of 1 October 2016.

Substance summary

Cetirizine hydrochloride is an orally active H_1-receptor antagonist and is indicated for relief of symptoms of seasonal allergic rhinitis.

Table 3.5: Chemical information

Property	cetirizine hydrochloride
CAS No.	83881-52-1
Chemical structure	 , 2 HCl and enantiomer
Chemical name	(*RS*)-2-[2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid dihydrochloride
Australian Approved Name (AAN)	cetirizine hydrochloride
Molecular Formula	$C_{21}H_{27}Cl_3N_2O_3$
Molecular Weight	461.8 g/mol
Form	white, crystalline powder
Solubility	water-soluble (160 g/100 mL)
Formulation	It is formulated as white, film-coated, scored 10 mg tablets, oral liquid 1 mg/mL and oral drops 10 mg/mL

Pre-meeting public submissions

Four (4) public submissions were received. One submission supported the proposal and three (3) submissions did not support the proposal.

The main point in support was:

- The proposed increase in pack size of unscheduled cetirizine hydrochloride is supported on the basis of cetirizine hydrochloride's safety profile, for consistency with loratadine, and for consistency with other similar markets.

The main points opposed were:

- There are other options readily available and also in the best interests of consumer safety.
- Do not believe the availability of cetirizine hydrochloride in a general retail setting should be expanded. A five- day supply pack should be adequate in providing for the general goals of treatment.
- Do not believe there is substantial public health benefit in widening the scheduling exemption for cetirizine hydrochloride.
- The use of cetirizine hydrochloride in pregnancy and breastfeeding is not recommended, and loratadine or short-acting antihistamines are preferred while breast feeding.

- Consumers need to be able to discuss with a healthcare professional/pharmacist the benefits and potential risks with taking cetirizine hydrochloride in managing allergic rhinitis. With healthcare professional involvement in allergic rhinitis management, the consumer experiences better outcomes than those who set their own treatment plans
- By allowing an exemption from scheduling, the access of cetirizine hydrochloride in an unregulated setting and where there is no healthcare professional available, this could lead to a higher incidence of adverse outcomes, negating any perceived positive benefit from greater access.
- Cetirizine hydrochloride and levocetirizine hydrochloride are currently listed on Appendix K (drugs required to be labelled with a sedation warning). If a medicine is deemed to be of sufficient risk that it must carry a warning label such as this, then it is not appropriate for sale in general retail with no access to professional advice.
- The additional sedation risk specific to cetirizine hydrochloride as evidenced by its listing on Appendix K makes it inappropriate for any further scheduling exemptions to be adopted. Based on evidence showing a higher incidence of drowsiness in cetirizine hydrochloride when compared to other second generation antihistamines such as loratadine and fexofenadine - higher risk of an adverse outcome from drowsiness - cautionary labels will not suffice.
- Lack of public need.
- Cetirizine hydrochloride is a medicine that can affect psychomotor (e.g. reaction times and hand-eye coordination) and cognitive functions (ability to make appropriate decisions), potentially having an adverse influence on the ability to drive.
  - Risk increased with combined with alcohol.
  - Risk of sedation and its potential impact on driving ability is best managed by facilitating access to professional advice via a Schedule 2 listing.
  - Warnings on packs insufficient – 21% of Australians have driven after taking sedative OTC medicines – should be supported by verbal information from medical professionals.
- Cetirizine hydrochloride more likely to result in sedation and impairment than other non-sedating (similarly effective) antihistamines.

Summary of ACMS advice to the delegate

The Committee advised that the Schedule 2 and Schedule 4 listing for cetirizine hydrochloride should be amended to include 10 days' supply.

The recommended wordings for the entries are as follows:

Schedule 4 – Amend Entry

CETIRIZINE HYDROCHLORIDE **except**:

a) when included in Schedule 2; or

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

iii) in a primary pack containing not more than ~~5~~ 10 days' supply; and

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

Schedule 2 – Amend Entry

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

a) in a primary pack containing not more than ~~5~~ 10 days' supply; and

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

The ACMS advised an implementation date of **1 June 2017.**

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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.

The reasons for the advice comprised the following:

- Adverse events associated with use of cetirizine hydrochloride during pregnancy or breastfeeding have been documented as low or nil and is managed through RASML. Increased benefit of increasing access to supply for indication, which is easy for consumers to self-diagnose, and improves patient autonomy. Rescheduling will align with other recent decisions for chemicals with a similar toxicological profile (loratadine and fexofenadine).
- The symptoms of seasonal allergic rhinitis (SAR) are easy for consumers to detect and self-diagnose and are generally short-term. It is noted that cetirizine hydrochloride may be used for other allergic disorders; however, this is unlikely to be problematic.
- Risks of cetirizine hydrochloride use include slight potential increase in somnolence compared with other less-sedating antihistamines. These effects are unlikely to be significant at the proposed doses. Adverse events associated with use during pregnancy/breast feeding have been documented but are negligible and managed by RASML requirements.
- Cetirizine hydrochloride requires a sedation warning, and dose is limited to 10 mg daily for use in adults and children 12 years of age and older.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that the Schedule 2 and Schedule 4 entries for cetirizine hydrochloride be amended from 5 days' supply to 10 days' supply.

The wording for the proposed schedule entries are as follows:

Schedule 4 –Amend Entry

CETIRIZINE HYDROCHLORIDE **except**:

a) when included in Schedule 2 ; or

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

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

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

Schedule 2 –Amend Entry

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

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

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

The proposed implementation date is **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- The benefits outweigh the risks.
- The symptoms of seasonal allergic rhinitis (SAR) are easy for consumers to detect and self-diagnose and are generally short-term. Increased benefit of increasing access to supply for indication, and improves patient autonomy.
- Adverse events associated with use of cetirizine hydrochloride are managed through labelling.
- Rescheduling will align with other recent decisions for similar chemicals (e.g. loratadine and fexofenadine).

Public submissions on the interim decision

Two (2) public submissions were received that supported the interim decision and the delegate's reasons for the decision. The main points were:

- Cetirizine hydrochloride has an excellent safety profile.
- Cetirizine hydrochloride has many years of in market experience with no significant safety issues.
- Cetirizine hydrochloride has similarity in safety, efficacy and tolerability profile to loratadine and fexofenadine .
- The decision is consistent with other similar global markets.
- The benefits of cetirizine hydrochloride outweigh the risks.

Delegate's final decision

The delegate has confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegate's final decision is that the Schedule 2 and Schedule 4 entries for cetirizine hydrochloride be amended from 5 days' supply to 10 days' supply with an implementation date of **1 June 2017**.

3.6 Tianeptine

Referred scheduling proposal

An application was submitted to include a new entry for tianeptine in Schedule 4.

Scheduling application

This was a delegate-initiated application. The delegate's proposed amendments to the Poisons Standard are as follows:

Schedule 4 – Proposed New Entry

TIANEPTINE.

The reason for the request is that tianeptine is currently being sold as a product name Stablon on at least one Australian website in powder form. Safety concerns have been raised that tianeptine is being abused, and poses a public health risk, requiring restrictions on its use.

Current scheduling status and relevant scheduling history

Tianeptine is not currently scheduled and has not been previously considered for scheduling; a scheduling history is not available.

Australian regulatory information

There have been several requests for special access of tianeptine in the past 10 years in Australia through the Special Access Scheme for Category B patients. Administration is usually by tablet, 37.5 mg – 75 mg daily, orally for twelve months.

Tianeptine is not an active in any products listed on the ARTG.

International regulatory information

Tianeptine is marketed as Stablon in 15 European Union countries (France, Luxembourg, Portugal, Bulgaria, Romania, Slovakia, Poland, Malta, Hungary, Lithuania, Slovenia, Czech Republic, Austria, Latvia, and Estonia) and in 66 countries throughout the world.

France: Authorised for marketing in February 1987. Tianeptine is included in List I, for prescription duration restricted to 28 days with overlap prescription prohibited except on the express instruction of the prescriber written on the prescription. Further conditions apply on pharmacist where a copy of the prescription is to be held for 3 years. It is also included on the list of medicines refundable by National Health Insurance.

Singapore: Stablon (tablet 12.5 mg tianeptine sodium) is a prescription-only drug under Licence No. SIN11182P. It is included in the First Schedule (special restrictions under Rule 10 apply) and the Third Schedule (substances required by Rule 15 (Additional Restrictions on sale of certain poisons) to be sold upon a prescription given by a medical practitioner, dentist or veterinary surgeons) of the Poisons Act.

Bahrain: The Drug Control Directorate has classified tianeptine sodium under the 'special-drugs under-controlled prescriptions' category due to increasing reports of misuse and abuse by patients.

No information could be located for US, Canada or New Zealand regulation for tianeptine.

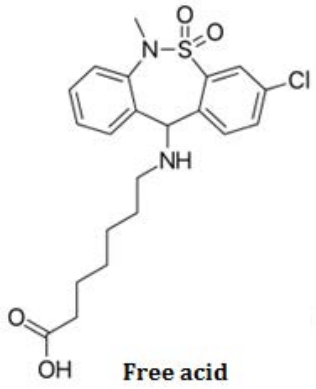
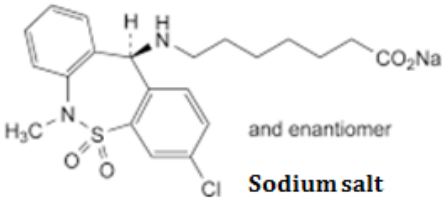
Substance summary

Tianeptine is a tricyclic compound with psycho-stimulant, anti-ulcer and anti-emetic properties. Tianeptine is considered as an anti-depressive agent and is used for treatment of major depressive disorder. Unlike other traditional anti-depressants that are selective serotonin reuptake inhibitors (SSRIs), tianeptine acts by increasing the presynaptic reuptake of serotonin and has indirect effects on alteration of glutamatergic receptors (AMDA and NMDA) activity. Reviews on the neurobiological activities of tianeptine, are attached.

Martindale states that tianeptine is given in oral doses of 12.5 mg, three times daily in treatment of depression. Doses should be reduced to a total of 25 mg daily in elderly patients. Isolated cases of hepatitis have been reported during treatment with tianeptine. Martindale also states that tianeptine has been reported to improve symptoms in patients with asthma. Martindale refers to reported misuse of tianeptine.

Tianeptine has one chiral centre and is present at the racemate. The stereocentre is at the C-11 position in the central thiazepinyl ring. Tianeptine differs chemically to other antidepressants by the presence of a sulphonamide function in the central nucleus and a lateral amino acid chain (see Table 3.6 for additional chemical information).

Table 3.6: Chemical information and other data

Property	Tianeptine (free acid)	Tianeptine sodium
CAS No.	66981-73-5 (online websites and Martindale) 72797-41-2 (Merck Index and SciFinder)	30123-17-2 (BP monograph and SciFinder)
Chemical structure	 Free acid	 and enantiomer **Sodium salt**
Molecular formula	$C_{21}H_{25}ClN_2O_4S$	$C_{21}H_{24}ClN_2NaO_4S$
Molecular Weight	436.9 g/mol	458.9 g/mol
Form	White solid	White or yellowish powder
Melting point	129 – 131°C	180°C
Chemical names	7-[(3-chloro-6,11-dihydro-6-methyl-5,5-dioxidodibenzo[c,f][1,2]thiazepin-11-yl)amino]-heptanoic acid	7-[(3-chloro-6,11-dihydro-6-methyl-5,5-dioxidodibenzo[c,f][1,2]thiazepin-11-yl)amino]-heptanoic acid monosodium salt (9CI)
British Approved Name (BAN)	N/A	Sodium 7-[[(11RS)-3-chloro-6-methyl-6,11-dihydrodibenzo[c,f][1,2]thiazepin-11-yl]amino]heptanoate S,S-dioxide
International trade names	Stablon; Coaxil; Tatiniol; Tianeurax; and Zinosal.	As for Tianeptine (free acid)

Property	Tianeptine (free acid)		Tianeptine sodium
WHO ATC Classification	N	Central nervous system	As for Tianeptine (free acid)
	N06	Psychoanaleptics	
	N06A	Anti-depressants	
	N06AX	Other Anti-depressants	
	N06AX14	Tianeptine	

Tianeptine is hygroscopic, and freely soluble in water. Tianeptine is amphoteric with two pK_a values, 4.4 (acidic) and 6.86 (basic), and is weakly lipophilic (log P at pH 7.4 = 1.06).

Literature[30] reports that absorption of tianeptine from tablet form is rapid and complete following oral administration to fasting healthy subjects. The mean C_{max} of tianeptine is 334 +/- 79 ng/mL. T_{max} is 0.94 +/- 0.47 h following oral administration. Absolute bioavailability is 99 +/- 29%. Tianeptine is rapidly and completely absorbed in the tablet form and is not subject to first-pass effect. Distribution of tianeptine in the body is characterized by the following: its rapidity, the mean distribution half-life being about 0.7 h; its limited extent, the apparent volume of distribution being about 0.8 L/kg (0.77 +/- 0.31 L/kg); and protein binding, which averages 93.8 +/- 2.4%. Elimination of tianeptine is characterized by a short mean half-life of 2 h 30 min (2.5 +/- 1.1 h) and by renal excretion of 0.4 ml/min (0.4 +/- 0.4 mL/min). Tianeptine is extensively metabolized. Major metabolites are analogues of tianeptine with a C5 and C3 lateral chain and an *N*-demethylated derivative. Studies have shown negligible influence on pharmacokinetic parameters of chronic alcoholism even in case of hepatic cirrhosis.

There is a BP/EP 2016 harmonised monograph for tianeptine sodium. There are no current USP monographs for Tianeptine or the Tianeptine Sodium. Online websites refer to both a sulfate and a sodium salt. The BP monograph for tianeptine sodium is transparent in relation to 4 impurities.

Pre-meeting public submissions

No pre-meeting submissions were received for tianeptine.

Summary of ACMS advice to the delegate

The Committee advised that tianeptine should be added to Schedule 4 and Appendix D Item 5.

The recommended wording for the entry is as follows:

Schedule 4 – New Entry

TIANEPTINE.

Appendix D item 5 – New Entry

TIANEPTINE.

The ACMS advised an implementation date of **1 June 2017.**

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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.

[30] Royer, R.J. *et al.,* Pharmacokinetics and metabolic parameters of tianeptine in healthy volunteers and in populations with risk factors. *Clin Neuropharmacol* 1988, 11 Suppl 2:S90-6 http://www.ncbi.nlm.nih.gov/pubmed/3180120

The reasons for the advice comprised the following:

- Clinical data suggest tianeptine as an effective antidepressant. It is used in 66 countries, but not in NZ, Canada, UK or US. In Singapore, tianeptine is only prescribed by psychiatrists. It is not registered or marketed in Australia. It is not in any products listed on ARTG and is not listed in Therapeutic Goods (permissible ingredients) Determination. Tianeptine is however freely available in Australia via websites where it is reportedly advertised as bulk powder.
- Tianeptine has a short half-life requiring 3 times daily dosing, so its use is likely to be very limited in a well-saturated market of once-a-day antidepressants. Glutamatergic pathways, in which tianeptine acts, may become important in future as research for cognitive enhancement and when neuroprotection develops. These pathways may also become an alternative antidepressant target for special populations (e.g. treatment resistant populations). Tianeptine has a wide therapeutic margin with minimal toxicity reported at very high doses.
- The benefits of tianeptine include its use as an antidepressant with other potential medical uses.
- The risks include misuse. It is apparently relatively uncommon and is apparently used for anxiolytic effect.
- In relation to potential for abuse, there are reports of opioid-like euphoria effects (from mu-agonist activity) at high doses (much higher than antidepressant effect e.g. 300–500 mg/day). There are some reports of abuse potential overseas and reports of 'doctor-shopping' in France, where 28 days' supply restrictions apply. Given this, tianeptine is recommended to have an Appendix D, item 5 listing.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal
- ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that a new Schedule 4 entry for tianeptine with an Appendix D item 5 entry is appropriate.

The proposed wording for the schedule and appendix entries is as follows:

Schedule 4 – New Entry

TIANEPTINE.

Appendix D item 5 – New Entry

TIANEPTINE.

The proposed implementation date is 1 **June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- The benefits outweigh the risks.
- Tianeptine has a short half-life requiring 3 times daily dosing, so its use is likely to be very limited in a well-saturated market of once-a-day antidepressants. Tianeptine has a wide therapeutic margin with minimal toxicity reported at very high doses.
- Tianeptine is an antidepressant available in Australia via websites where it is reportedly advertised as bulk powder. The risks of misuse are apparently relatively uncommon.
- There are reports of opioid-like euphoria effects (from mu-agonist activity) at high doses (much higher than antidepressant effect e.g. 300–500 mg/day). There are some reports of abuse potential overseas and 'doctor-shopping'. Given this, tianeptine is recommended to have an Appendix D, item 5 listing.

Public submissions on the interim decision

No public submissions were received in response to the interim decision for tianeptine.

Delegate's final decision

The delegate has confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegate's final decision is to create new Schedule 4 and Appendix D Item 5 entries for tianeptine with an implementation date of **1 June 2017**.

3.7 Olaparib

Referred scheduling proposal

A New Chemical Entity (NCE) delegate from the Therapeutic Goods Administration has referred the substance olaparib, proposing that it be listed in Appendix L with warning statement 62 – Do not use if pregnant.

Scheduling application

The proposed amendment to the Poisons Standard is as follows:

Schedule 4 – Proposed New Entry

OLAPARIB.

Appendix L – Proposed New Entry

OLAPARIB.

62 - Do not use if pregnant.

The reasons provided by the clinical delegate are based on its mechanism of action (PARP inhibition), LYNPARZA (olaparib) could cause foetal harm when administered to pregnant woman. Studies in rats have shown that olaparib causes embryofoetal lethality and induces major foetal malformations (major eye and vertebral/rib malformations) at exposures below those expected at the recommended human dose of 400 mg twice daily.

While this is currently approved for women who have had ovarian cancer (and will have had hysterectomy, salpingo-oophorectomy), there are proposed extensions of indications and the scheduling may not be reviewed again. This is a sensitive issue, as obviously such women cannot become pregnant.

Current scheduling status and relevant scheduling history

Olaparib is not currently scheduled and has not been previously considered for scheduling; a scheduling history is therefore not available.

Australian regulatory information

Olaparib is the active ingredient in one ARTG entry (product name Lynparza, AUST R 234008), formulated as a 50 mg capsule bottle by AstraZeneca Pty Ltd and registered on 13 October 2016.

International regulatory information

Olaparib is not classified in New Zealand. In the USA and Canada, olaparib is a Prescription Only medicine.

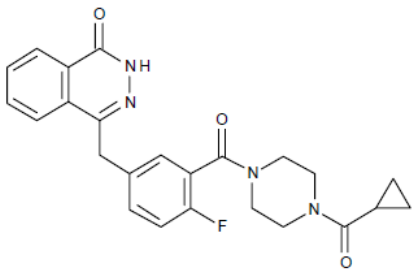
Substance summary

Olaparib is an inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3) and is indicated as monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed BRCA-mutated (germline or somatic) high grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer who have responded (complete response or partial response) after platinum-based chemotherapy. Prior treatment must have included at least 2 courses of platinum-based regimens.

Chemical information for olaparib is shown in Table 3.7. Several polymorphs of olaparib are reported. Olaparib is a non-hygroscopic crystalline powder, stable in the A form (non-solvated polymorph). There are no potential olaparib isomers except for tautomers of the phthalazinone which are likely to strongly favouring one form in solution. The pK_a has been calculated to be -1.16 (basic) and 12.07 (acidic) on the phthalazinone moiety. Given this, olaparib would be unionised across the physiological pH range. Solubility is independent of pH.

The structure is not closely related to registered kinase inhibitors, nor to veliparib (an experimental PARP inhibitor). There are no official monographs for olaparib.

Table 3.7: Chemical information

Property	Olaparib
CAS No.	763113-22-0
Chemical structure	
Chemical name	4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one
Molecular formula	$C_{24}H_{23}FN_4O_3$
Molecular weight	434.5 g/mol
Melting point	206°C
Chirality	achiral

Property	Olaparib
Origin	synthetic
Solubility	Low
BCS*	Class IV (low solubility, low permeability)

*Biopharmaceutical Classification System

Pre-meeting public submissions

One public submission was received and supported the proposal. No additional reasons for the support were provided.

Summary of ACMS advice to the delegate

The Committee advised that a new Schedule 4 entry for olaparib without an Appendix L entry is appropriate.

The recommended wording for the entry is as follows:

Schedule 4 – New Entry

OLAPARIB.

The ACMS advised an implementation date of **1 June 2017.**

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the advice comprised the following:

- The risks of olaparib use include high potential for foetal death and/or malformations as has been shown in animal studies.
- The approved purposes for use of olaparib would exclude pregnancy, but there is potential for other approved and off-label uses in the future. Furthermore, the approved purpose for use of olaparib may cause distress if exclusion of pregnancy is included on the label. Olaparib should only be prescribed by oncology specialists who will appropriately counsel women about risks in pregnancy (if clinically relevant). Currently olaparib is very unlikely to be used in women with childbearing potential, as olaparib is only being used in patients with ovarian cancer.
- Anti-neoplastic agents are not routinely included in Appendix L or Appendix D with pregnancy warning, despite teratogenicity and other foetal abnormalities being a common concern with this class of drugs.
- There is some labelling inconsistency amongst oncology agents. Labelling with warning statements may be revisited with additional use approval.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal
- Public submissions received

- ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that a new Schedule 4 entry for olaparib without an Appendix L entry is appropriate.

The proposed wording for the schedule entry is as follows:

Schedule 4 — New Entry

OLAPARIB.

The proposed implementation date is **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Anti-neoplastic agents are not routinely included in Appendix L or Appendix D with a pregnancy warning, despite teratogenicity and other foetal abnormalities being a common concern with this class of drugs.
- Olaparib should only be prescribed by oncology specialists who will appropriately counsel women about risks in pregnancy.

Public submissions on the interim decision

No public submissions were received in response to the interim decision for olaparib.

Delegate's final decision

The delegate has confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegate's final decision is to create a new Schedule 4 entry for olaparib without an Appendix L entry with an implementation ate of **1 June 2017**.

3.8 Ceritinib

Referred scheduling proposal

A New Chemical Entity (NCE) delegate from the Therapeutic Goods Administration has referred the substance ceritinib, proposing that the substance be listed in Appendix L with warning statement 62 – Do not use if pregnant.

Scheduling application

The proposed amendment to the Poisons Standard is as follows:

Schedule 4 – Proposed New Entry

CERITINIB.

Appendix L – Proposed New Entry

CERITINIB.

62 - Do not use if pregnant

The reason provided by the clinical delegate is on the basis that there are no human data, but in animals, embryofoetal toxicity occurred at very low exposures (as low as 0.2-fold exposure intended in humans).

Current scheduling status and relevant scheduling history

Ceritinib is not currently scheduled in Australia and has not been previously considered for scheduling; a scheduling history is therefore not available.

Australian regulatory information

One registered product containing ceritinib (150 mg) was entered onto the ARTG on 16 September 2016. It is available for use as an active ingredient in prescription medicines but not available as an excipient or equivalent ingredient in any application.

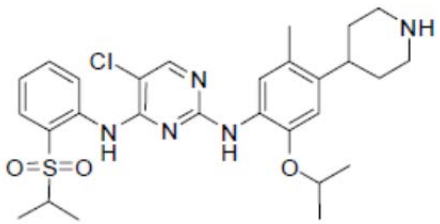
International regulatory information

Ceritinib lactate is not classified in New Zealand. In the USA and Canada, ceritinib is a Prescription Only Medicine.

Substance summary

Ceritinib is an inhibitor of anaplastic lymphoma kinase (ALK). The ALK inhibitor works against the ALK translocation involved in the development of certain cancers.

Table 3.8: Chemical information

Property	Ceritinib
CAS No.	1032900-25-6
Chemical structure	
Chemical name	5-chloro-2-*N*-{5-methyl-4-(piperidin-4-yl)-2-[(propan-2-yl)oxy]phenyl}-4-N-[2-(propane-2-sulfonyl) phenyl]pyrimidine-2,4-diamine
Molecular formula	$C_{28}H_{36}ClN_5O_3S$
Molecular weight	558.1 g/mol
Origin	Synthetic
Form	White to almost white or light yellow or light brown powder
Solubility	Good solubility in very acidic aqueous medium. The solubility decreases significantly with increasing pH. Good solubility is achieved in methanol.

Property	Ceritinib
pH	6.86 (in 1% water)
Melting point	174°C
pK_a	4.1 and 9.7
Biopharmaceutical Classification System (BCS) status	Class IV (Low Permeability, Low Solubility)
Isomerism	Ceritinib shows no isomerism with two known polymorphs.

Ceritinib is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on or who are intolerant of crizotinib. This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease-related symptoms has not been established.

Pre-meeting public submissions

Two public submissions were received, one submission supported the Appendix L entry, with warning statement 62 – 'Do not use if pregnant', and one submission did not support the proposal.

The main points in opposition were:

- Recent oncology approvals for Category X medicines vismodegib and sonidegib and Category D medicine crizotinib are not in Appendix L. The proposal to include ceritinib in Appendix L appears to not be applied to substances with a similar or greater risk profile.
- The PI does not have a contraindication. The approved PI states *"ZYKADIA should not be given to a pregnant women unless the potential benefits for her outweigh the potential risk to the fetus."*. "*If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus."*
- The PI and CMI clearly state risk/benefits of taking the drug while pregnant. Both PI and CMI state highly effective contraception should be used. PI states: "*Women of childbearing potential should be advised to use a highly effective method of contraception noting the potential for ceritinib to decrease the effectiveness of the oral contraceptive (see Interactions with Other Medicines) while receiving ZYKADIA and for up to 3 months after discontinuing treatment.*"
- Patients must be under the care of a specialist in order to be prescribed this drug. It is the physician's role and responsibility to discuss with their patients the risks associated with these medicines even though the risk of pregnancy is low in both patient populations.

Summary of ACMS advice to the delegate

The Committee advised that ceritinib be entered in Schedule 4 without an Appendix L entry.

The recommended wording for the entry is as follows:

Schedule 4 –New Entry

CERITINIB.

The ACMS recommended an implementation date of **1 June 2017**.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the advice comprised the following:

- Although there is no human data, pregnant rats and rabbits given ceritinib had increased skeletal abnormalities during organogenesis as well as a low incidence of visceral anomalies.
- The benefits of ceritinib use include its efficacy as a second line therapy for people who are intolerant or show disease progression with first-line therapy.
- The risks of olaparib include embryofoetal toxicity at very low exposure in animals.
- Generally Appendix L would not be applied to anti-neoplastics when patients are being counselled to avoid pregnancy in the treatment period and shortly thereafter.
- The purpose for olaparib is treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) where the disease has progressed on or who are intolerant of crizotinib (which has similar mechanism of action). Only a small number of patients would require ceritinib as its use is narrow (as a chemotherapeutic agent for NSCLC). Use of ceritinib will be prescribed only by specialist oncologists to patients under ongoing specialist care.
- Adverse events most common for ceritinib include gastrointestinal disorders (diarrhoea, nausea, vomiting, abdominal pain). Other very common adverse reactions include decreased appetite, fatigue, liver laboratory test abnormalities, abdominal pain and rash, as well as possible foetal toxicity.
- Antineoplastic agents are not routinely included in Appendix L or Appendix D with pregnancy warnings despite teratogenicity and other foetal abnormalities being a common concern with this class of drugs. The dosage formulation is 150 mg oral capsules taken daily, and its use will be closely monitored by specialists. Therefore, the issue of pregnancy should be raised by treating clinicians.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that a new Schedule 4 entry for ceritinib without an Appendix L entry is appropriate.

The proposed wording for the schedule entry is as follows:

Schedule 4 — New Entry

CERITINIB.

The proposed implementation date is **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Anti-neoplastic agents are not routinely included in Appendix L or Appendix D with a pregnancy warning, despite teratogenicity and other foetal abnormalities being a common concern with this class of drugs.
- Ceritinib should only be prescribed by oncology specialists who will appropriately counsel women about risks in pregnancy.

Public submissions on the interim decision

No public submissions were received in response to the interim decision for ceritinib.

Delegate's final decision

The delegate has confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegate's final decision is to create a new Schedule 4 entry for ceritinib without an Appendix L entry to be implemented on **1 June 2017**.

3.9 Panobinostat lactate

Referred scheduling proposal

A delegate from the Therapeutic Goods Administration has referred the substance panobinostat lactate, a new chemical entity (NCE), proposing that it be listed in Appendix L with warning statement 62 – Do not use if pregnant.

Scheduling application

The proposed amendment to the Poisons Standard is as follows:

Schedule 4 – Proposed New Entry

PANOBINOSTAT.

Appendix L – Proposed New Entry

PANOBINOSTAT.

62 - Do not use if pregnant.

The reason provided by the clinical delegate is on the basis that the effects of panobinostat are unknown in humans, but there is evidence of maternal toxicities, embryo-foetal lethality and malformations in two species, including at 0.5 times the proposed clinical exposure in rabbits in the nonclinical studies.

Other consideration: There is a boxed warning to alert prescribers and consumers to the potentially multiple and severe toxicities that may occur with this medicine. The indication was restricted to those with very limited remaining treatment options and includes the following statement: Treatment should be initiated and monitored by a specialist with experience in treating haematological malignancies.

Current scheduling status and relevant scheduling history

Panobinostat lactate is not currently scheduled and has not been previously considered for scheduling; a scheduling history is therefore not available.

Australian regulatory information

Panobinostat lactate is as an active ingredient in Farydak (Novartis Pharmaceuticals Australia Pty Ltd) as 10 mg, 15 mg and 20 mg capsules (AUST R. 229941, 230844 and 230845 respectively), registered on 31 March 2016.

International regulatory information

Panobinostat lactate is not classified in New Zealand or Canada. In the USA, panobinostat lactate is a Prescription Only medicine.

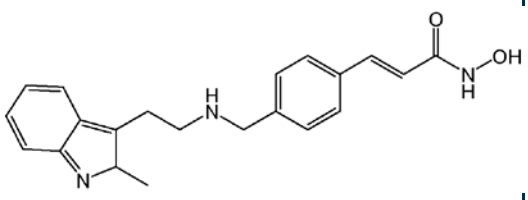
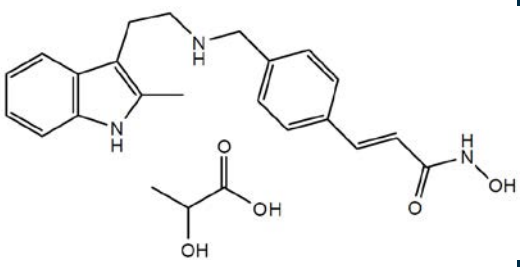
Substance summary

Panobinostat lactate, in combination with bortezomib and dexamethasone, is indicated for the treatment of adult patients with relapsed and/or refractory multiple myeloma, who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent. Treatment should be initiated and monitored by a specialist with experience in treating haematological malignancies.

Panobinostat lactate is a pan-inhibitor of Class I, II, and IV histone (and non-histone) deacetylases (HDACs/DACs).

While the free base of panobinostat has no chiral centres, the lactic acid is chiral and the racemate of lactic acid is used to prepare panobinostat lactate. The panobinostat double bond has controlled *E* (trans) stereochemistry. Panobinostat has a hydroxamic acid group (-CONHOH). See Table 3.9 for additional chemical information on panobinostat and panobinostat lactate.

Table 3.9: Chemical information

Property	Panobinostat (free base)	Panobinostat lactate
CAS No.	404950-80-7	960055-68-9
Chemical structure		
Molecular Formula	$C_{21}H_{23}N_3O_2$	$C_{21}H_{23}N_3O_2.C_3H_6O_3$
Molecular weight	349.4 g/mol	439.5 g/mol
Chemical name	3-[4-[2-(2-methyl-1*H*-indol-3-yl)ethylaminomethyl]phenyl]-2(*E*)-propenohydroxamic acid	(2*E*)-*N*-hydroxy-3-[4-({[2-(2-methyl-1*H*-indol-3-yl)ethyl]amino}methyl)phenyl]-2-propenamide 2-hydroxypropanoate (1:1)
IUPAC name	(*E*)-N-hydroxy-3-[4-[[2-(2-methyl-1*H*-indol-3-yl)ethylamino]methyl]phenyl]prop-2-enamide	(*E*)-*N*-hydroxy-3-[4-[[2-(2-methyl-1*H*-indol-3-yl)ethylamino]methyl]phenyl]prop-2-enamide;2-hydroxypropanoic acid
Origin and form	Synthetic; yellow solid	Synthetic; stable; crystalline (one known polymorph)

Property	Panobinostat (free base)	Panobinostat lactate
Melting point	-	175°C
pK_a	8.4 and 9.0 (alkaline)	-
Solubility	-	The aqueous solubility of panobinostat lactate is pH dependent, with maximum solubility at pH 2 or 3 (~ 5 mg/mL) and low solubility at neutral pH (0.3 mg/mL at pH 6.8); low solubility at pH 7.6 (0.07 mg/mL)
Biopharmaceutics Classification System (BCS)	-	Class II (low solubility, high permeability).*

* The solubility classification is borderline high.

Pre-meeting public submissions

Two public submissions were received. One submission supported the Appendix L entry, with warning statement 62 – 'Do not use if pregnant'; and one submission did not support the proposal. The main points in opposition of the proposal were:

- Recent oncology approvals for Category X medicines vismodegib and sonidegib and Category D medicine crizotinib are not in Appendix L. The proposal to include panobinostat in Appendix L appears to not be applied to substances with a similar or greater risk profile.
- The approved PI does not have a contraindication. The approved PI states "The patient should be advised of the risk to a fetus, if FARYDAK is used during pregnancy or if the patient becomes pregnant while taking this drug".
- The PI and CMI clearly state risk/benefits of taking the drug while pregnant. Both PI and CMI state highly effective contraception should be used. PI states: *"Sexually-active females of reproductive potential should have a pregnancy test prior to the initiation of treatment with FARYDAK". "Women of child-bearing potential should be advised to use a highly effective method of contraception (methods that result in less than 1% pregnancy rates) during treatment with FARYDAK and for 3 months after the last dose of FARYDAK";* and
- Patients must be under the care of a specialist in order to be prescribed this drug. It is the physician's role and responsibility to discuss with their patients the risks associated with these medicines even though the risk of pregnancy is low in both patient populations.

Summary of ACMS advice to the delegate

The Committee advised that panobinostat should be entered in Schedule 4 without an Appendix L entry.

The recommended wording for the entry is as follows:

Schedule 4 – New Entry

PANOBINOSTAT.

The ACMS advised an implementation date of **1 June 2017.**

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the advice comprised the following:

- The risk of panobinostat to a human foetus is unknown. Data suggests high risk of foetal malformation or non-viability in animal trials at half the dose used in humans.
- Panobinostat was registered as a Prescription-only Medicine by the TGA in March 2016 as an adjunctive therapy in adults with refractory multiple myelomas who have not responded to treatment with at least two prior regimens, including bortezomib and an immunomodulatory agent. Therefore the potential patient population is low.
- The product contains a boxed warning to alert prescribers and consumers to the potentially multiple and severe toxicities that may occur with this medicine. The indication was restricted to those with very limited remaining treatment options and includes the following statement: Treatment should be initiated and monitored by a specialist with experience in treating haematological malignancies.
- Generally, Appendix L would not be applied to anti-neoplastics when patients are already being counselled to avoid pregnancy in the treatment period and shortly afterwards. Antineoplastic agents are not routinely included in Appendix L or Appendix D with pregnancy warnings despite teratogenicity and other foetal abnormalities being a common concern with this class of drugs

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that a new Schedule 4 entry for panobinostat without an Appendix L entry is appropriate.

The proposed wording for the schedule entry is as follows:

Schedule 4 — New Entry

PANOBINOSTAT.

The proposed implementation date is **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.

- Anti-neoplastic agents are not routinely included in Appendix L or Appendix D with a pregnancy warning, despite teratogenicity and other foetal abnormalities being a common concern with this class of drugs.
- Panobinostat should only be prescribed by oncology specialists who will appropriately counsel women about risks in pregnancy.

Public submissions on the interim decision

No public submissions were received in response to the interim decision for panobinostat lactate.

Delegate's final decision

The delegate has confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegate's final decision is to create a new Schedule 4 entry for panobinostat without an Appendix L entry to be implemented on **1 June 2017**.

3.10 Brivaracetam

Referred scheduling proposal

A New Chemical Entity (NCE) delegate from the Therapeutic Goods Administration has referred the substance brivaracetam, proposing that the substance be listed in Appendix K.

Scheduling application

The proposed amendment to the Poisons Standard is as follows:

Schedule 4 – Proposed New Entry

BRIVARACETAM.

Appendix K – Proposed New Entry

BRIVARACETAM.

The reason provided by the clinical delegate is that brivaracetam is an antiepileptic medicine causing sedation.

Current scheduling status and relevant scheduling history

Brivaracetam is not currently scheduled in Australia and has not been previously considered for scheduling; a scheduling history is therefore not available.

Australian regulatory information

Brivaracetam is registered (product name Briviact) on the ARTG (as of 4 August 2016) for use as add-on therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients from 16 years of age with epilepsy. Briviact (UCB Australia Pty Ltd T/A UCB Pharma Division of UCB Australia) is available as:

- 10 mg, 25 mg, 50 mg, 75 mg and 100 mg film-coated tablets (AUST R. 243794, 243796, 243797, 243798 and 243792 respectively);
- 50 mg/5 mL injection vial (AUST R. 243795); and
- 10 mg/mL oral solution bottle (AUST R. 243793)

International regulatory information

Brivaracetam is not classified in New Zealand. In the USA and Canada, brivaracetam is classified as a Prescription Only medicine.

Substance summary

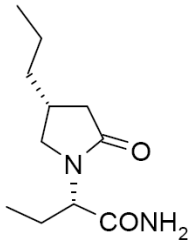
Brivaracetam is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients from 16 years of age with epilepsy.

As a 4-*n*-propyl analogue of levetiracetam, brivaracetam is also a Synaptic Vesicle Glycoprotein 2A (SV2A) anti-seizure/anti-epileptic drug, displaying a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain. Binding to SV2A is considered to be the primary mechanism for brivaracetam anticonvulsant activity, however, the precise mechanism by which brivaracetam exerts is anticonvulsant activity has not been fully elucidated. Brivaracetam did not act via Na^+ channels in normal adult neurons and may act, in part, by inhibiting *N*-methyl-D-aspartate (NMDA) excitatory pathways and disinhibiting gamma-amino butyric acid (GABA) and glycine inhibitory pathways.

Brivaracetam has 2 chiral centres associated with C2 of the butanamide group and C4 of the 2-oxo-4-(1-propyl)pyrrolidine ring. Two polymorphs of brivaracetam are reported. Brivaracetam is highly soluble and is Class I according to the Biopharmaceutical Classification System (BCS) (Table 3.10).

The pharmacokinetic profile of brivaracetam is favourable and linear, and it undergoes extensive metabolism into inactive compounds, mainly through the hydrolysis of its acetamide group. Furthermore, it does not significantly interact with other antiepileptic drugs and more than 95% is excreted through the urine, with an unchanged fraction of 8%–11%.

Table 3.10: Chemical information

Property	Brivaracetam
CAS No.	357336-20-0
Chemical structure	
Chemical name	(2*S*)-2-[(4*R*)-2-oxo-4-propyltetrahydro-1*H*-pyrrol-1-yl]butanamide
Molecular Formula	$C_{11}H_{20}N_2O_2$
Molecular weight	212.3 g/mol
pK_a	Brivaracetam has no ionisable centres, so pK_a cannot be measured.
Origin	Synthetic
Form	White to off-white crystalline powder
Solubility	It is very soluble in water, buffer (pH 1.2, 4.5 and 7.4), ethanol, methanol, and glacial acetic acid. Brivaracetam is freely soluble in acetonitrile and acetone and soluble in toluene. It is very slightly soluble in *n*-hexane.
BCS status	Class 1

Pre-meeting public submissions

One public submission was received and supported the proposal. No reasons were given.

Summary of ACMS advice to the delegate

The Committee advised that brivaracetam should be entered in Schedule 4 with an Appendix K entry.

The recommended wording for brivaracetam is as follows:

Schedule 4 – New Entry

BRIVARACETAM.

Appendix K – New Entry

BRIVARACETAM.

The Committee recommended an implementation date of **1 June 2017.**

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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.

The reasons for the advice comprised the following:

- The benefit for brivaracetam is that, as a newly-registered drug, it is an add-on therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy, from 16 years of age. The purpose is appropriate; clinical efficacy seems adequate.
- The risks and toxicity of brivaracetam are listed in the Clinical Evaluation Report (CER). However, somnolence, dizziness and fatigue are important risks to consider in relation to including brivaracetam in Appendix K. Inclusion in Appendix K would permit pharmacists to apply statements that are appropriate. Clinical safety at the doses suggested is adequately documented.
- The benefits outweigh the risks for this indication. Documentation provided by the applicant is considered adequate.
- Brivaracetam is available as tablets with 10 mg, 25 mg, 50 mg, 75 mg, 100 mg; 10 mg/mL oral solution and 50 mg/5 mL solution for injection. This is a prescription medicine. The Appendix K entry would require pharmacists to include sedation warning statements on dispensed medicines. CMI will be made available as per TGA requirements. The dosage, formulation, labelling and packaging is appropriate and similar to overseas applications.
- The CER states that there were no reports of abuse, misuse, dependence or withdrawal with brivaracetam in the clinical studies.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that a new Schedule 4 entry for brivaracetam with an Appendix K entry is appropriate.

The proposed wording for the schedule and appendix entries is as follows:

Schedule 4 –New Entry

BRIVARACETAM.

Appendix K –New Entry

BRIVARACETAM

The proposed implementation date is **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Brivaracetam is an additional therapy for epilepsy in patients from 16 years of age.
- The benefits outweigh the risks for this indication.
- Somnolence, dizziness and fatigue are important risks to consider. Brivaracetam is a prescription medicine available as tablets, as an oral solution and for injection. The Appendix K entry would require pharmacists to include sedation warning statements on dispensed medicines.

Public submissions on the interim decision

No public submissions were received in response to the interim decision for brivaracetam.

Delegate's final decision

The delegate has confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegate's final decision is to create new Schedule 4 and Appendix K entries for brivaracetam with an implementation date of **1 June 2017**.

3.11 Guanfacine hydrochloride

Referred scheduling proposal

The New Chemical Entity (NCE) delegate from the Therapeutic Goods Administration has referred the substance guanfacine hydrochloride, proposing that the substance be listed in Appendix K.

Scheduling application

The proposed amendment to the Poisons Standard is as follows:

Schedule 4 – Proposed New Entry

GUANFACINE HYDROCHLORIDE.

Appendix K – Proposed New Entry

GUANFACINE HYDROCHLORIDE

The reason provided by the clinical delegate is on the basis that guanfacine hydrochloride causes sedation.

Current scheduling status and relevant scheduling history

Guanfacine hydrochloride is not currently scheduled in Australia and has not been previously considered for scheduling; a scheduling history is therefore not available.

International regulatory information

Guanfacine hydrochloride is not classified in New Zealand. In the USA and Canada, Guanfacine hydrochloride is classified as a Prescription Only medicine.

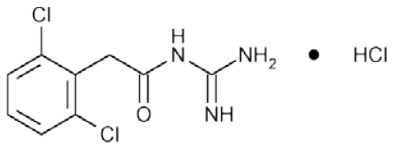
Substance summary

Guanfacine hydrochloride is a central alpha$_{2A}$-adrenergic receptor agonist and is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in paediatric patients (children and adolescents 6-17 years old inclusive).

Guanfacine hydrochloride is not a central nervous system (CNS) stimulant, a monoamine transporter inhibitor or releaser of presynaptic dopamine or norepinephrine. The mode of action of guanfacine hydrochloride in ADHD is not fully established. Preclinical research suggests guanfacine hydrochloride modulates signalling in the prefrontal cortex and basal ganglia through direct modification of synaptic norepinephrine transmission at the alpha 2-adrenergic receptors. The INN is guanfacine[31].

There is a USP 36 monograph for guanfacine hydrochloride, but no BP 2016 monograph.

Table 3.11: Chemical information

Property	Guanfacine hydrochloride
CAS No.	29110-48-3
Chemical structure	
Chemical name	*N*-amidino-2-(2,6-dichlorophenyl)acetamide monohydrochloride
Australian Approved Name (AAN)	guanfacine hydrochloride (reference USP, USAN)
Molecular formula	$C_9H_9Cl_2N_3O.HCl$
Molecular weight	282.6 g/mol (for the hydrochloride salt)
Form	White to off-white powder (single polymorphic form)
Solubility	sparingly soluble in water and alcohol and slightly soluble in acetone
partition coefficient (logP)	2-octanol/water: 0.10
Dissociation constant	7.69

[31] http://www.who.int/substance_abuse/publications/opioid_dependence_guidelines.pdf?ua=1 and http://apps.who.int/iris/bitstream/10665/68742/1/WHO_EDM_QSM_2004.5.pdf?ua=1

Property	Guanfacine hydrochloride
pH	~4 when dissolved in water

Pre-meeting public submissions

No pre-meeting submissions were received for guanfacine.

Summary of ACMS advice to the delegate

The Committee advised that guanfacine should be entered in Schedule 4 with an Appendix K listing.

The recommended wording for the guanfacine entry is as follows:

Schedule 4 –New Entry

GUANFACINE.

Appendix K –New Entry

GUANFACINE.

The Committee also recommended an implementation date of **1 June 2017**.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (a) the risks and benefits of the use of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the advice comprised the following:

- Guanfacine is a central alpha$_{2A}$-adrenergic receptor agonist used in the treatment of ADHD in children and adolescents.
- Guanfacine hydrochloride carries a significant risk of causing sedation and somnolence in humans exhibited by a medicine in normal use. Data demonstrates impairment of critical motor reflexes and cognitive skills applicable to driving or the operation of machinery with guanfacine hydrochloride use and therefore there is a need to warn users of any potential danger of the medication.
- There are no products containing guanfacine hydrochloride currently registered in the ARTG. This is a prescription-only medicine and Appendix K sedation warning is appropriate.
- Guanfacine hydrochloride has no known potential for abuse or dependence. The current sedation warning statements are more appropriate for a medication used in adults rather than children and adolescents.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal
- ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that a new Schedule 4 entry for guanfacine with an Appendix K listing is appropriate.

The proposed wording for the schedule and appendix entries is as follows:

Schedule 4 – New Entry

GUANFACINE.

Appendix K – New Entry

GUANFACINE

The proposed implementation date is **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (a) the risks and benefits of the use of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Guanfacine hydrochloride has a significant risk of causing sedation.

Public submissions on the interim decision

No public submissions were received in response to the interim decision for guanfacine hydrochloride.

Delegate's final decision

The delegate has confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegate's final decision is to create new Schedule 4 and Appendix K entries for guanfacine with an implementation date of **1 June 2017**.

3.12 Follitropin delta

Referred scheduling proposal

A New Chemical Entity (NCE) delegate from the Therapeutic Goods Administration has referred the substance follitropin delta, proposing that the substance be listed in Appendix D, Item 1 – Poisons available only from or on the prescription or order of an authorised medical practitioner.

Scheduling application

The proposed amendment to the Poisons Standard is as follows:

Schedule 4 – Proposed New Entry

FOLLITROPIN DELTA.

Appendix D – Proposed New Entry

FOLLITROPIN DELTA for human use.

Item 1 – Poisons available only from or on the prescription or order of an authorised medical practitioner.

The reason provided by the clinical delegate is that follitropin delta should only be prescribed by specialist medical practitioners (e.g., FRANZCOG, FRCOG) in respect of particular patients, following endocrine function tests carried out at an endocrine laboratory - as for other follitropins (alpha and beta).

Current scheduling status and relevant scheduling history

Follitropin delta is not currently scheduled in Australia; however, the analogues follitropin alpha and follitropin beta are currently in the Poisons Standard as follows:

Schedule 4

FOLLITROPIN ALPHA.

FOLLITROPIN BETA.

Appendix D, Item 1 – Poisons available only from or on the prescription or order of an authorised medical practitioner.

FOLLITROPIN ALPHA (recombinant human follicle-stimulating hormone) for human use.

FOLLITROPIN BETA (recombinant human follicle-stimulating hormone) for human use.

Index

FOLLITROPIN ALPHA
cross reference: FOLLICLE-STIMULATING HORMONE, RECOMBINANT HUMAN

FOLLITROPIN BETA
cross reference: FOLLICLE-STIMULATING HORMONE, RECOMBINANT HUMAN

Australian regulatory information

No products containing follitropin delta are on the Australian Register of Therapeutic Goods (ARTG). Currently registered products containing follitropin alpha or follitropin beta on the ARTG are tabulated below.

Table 3.12A: ARTG entries for follitropin alpha and follitropin beta

Active ingredient/s	Drug name	Additional actives	Relevant ARTG IDs	Formulation	Sponsor
Follitropin alpha	AFOLIA	N/A	262649, 262648, 262647, 262646, 262645.	5.5, 11, 16.5, 22 and 33 mg; solution for injection cartridge in a pre-filled pen.	Finox Biotech Australia Pty Ltd
Follitropin alpha	BEMFOLA	N/A	231053, 231052, 231051, 231046, 231039.	5.5, 11, 16.5, 22 and 33 mg; solution for injection cartridge in a pre-filled pen	Finox Biotech Australia Pty Ltd
Follitropin alpha	GONAL-F	N/A	96237, 96236, 96230, 96114, 93043, 91564, 91563, 91562, 81623.	37.5 IU (2.73 mg), 75 IU (5.46 mg), 150 IU (10.92 mg), 300IU /0.5mL (21.84 mg), 450IU /0.75mL (32.76 mg), 900IU /1.5mL (65.52 mg); and 45 and 1050 IU (retrievable dose); solution for injection cartridge, pre-assembled in a pen; powder for injection vial with diluent vial/syringe; and/or multidose powder for injection vial with diluent pre-filled syringe.	Merck Serono Australia Pty Ltd
Follitropin alpha	PERGOVERIS	Lutropin alpha	152797.	150 IU / 75 IU; powder for injection vial with diluent vial.	Merck Serono Australia Pty Ltd

Active ingredient/s	Drug name	Additional actives	Relevant ARTG IDs	Formulation	Sponsor
Follitropin beta	PUREGON	N/A	76437, 76436, 70858, 70857, 70856, 116843, 116842.	50 IU/0.5mL, 100 IU/0.5mL, 150 IU/0.5mL, 300 IU, 600 IU, 900 IU; solution for injection cartridge, solution for injection vial.	Merck Sharp & Dohme Australia Pty Ltd

International regulatory information

Follitropin delta is not classified in New Zealand and does not appear to be an approved drug product in the USA or Canada. However, follitropin alpha and follitropin beta are approved as follows:

The US FDA:

Drug name	Active ingredient/s
Bravelle	Urofollitropin
Fertinex	Urofollitropin
Follistim	Urofollitropin alfa/beta
Follistim AQ	Urofollitropin alfa/beta
Gonal-F	Urofollitropin alfa/beta
Gonal-F RFF	Urofollitropin alfa/beta
Gonal-F RFF REDI-JECT	Urofollitropin alfa/beta
Metrodin	Urofollitropin

Canada: In Canada there are three prescription products for human use containing follitropin alfa as the active ingredient (Gonal-F, Gonal-F Pen and Pergoveris, multiple presentations); and one prescription product for human use containing follitropin beta as the active ingredient (Puregon, multiple presentations).

Substance summary

Follitropin delta is a novel human recombinant follicle-stimulating hormone indicated for controlled ovarian stimulation for the development of multiple follicles in women undergoing assisted reproductive technology (ART) therapy such as *in vitro* fertilisation (IVF) or intra-cytoplasmic sperm injection (ICSI). The most important effect resulting from parenteral administration of FSH is the development of multiple mature follicles.

Follitropin delta is a recombinant human follicle-stimulating hormone (FSH) produced in a human cell line (PER.C6®) by recombinant DNA technology. Follitropin delta is a heterodimer composed of one α and one β subunit (Table 3.12B).

Table 3.12B: Chemical information

Property	Follitropin delta	
CAS No.	146479-72-3	
Form	Clear and colourless in solution (pH 6.0–7.5)	
Subunit	**FSH subunit α**	**FSH subunit β**
Amino acid sequence (***N*** – indicates glycosylation sites of the mature α and β subunits)	1 APDVQDCPEC TLQENPFFSQ PGAPILQCMG CCFSRAYPTP LRSKKTMLVQ K***N***VTSESTCC 61 VAKSYNRVTV MGGFKVE***N***HT ACHCSTCYYH KS	1 NSCELT***N***ITI AIEKEECRFC ISI***N***TTWCAG YCYTRDLVYK DPARPKIQKT CTFKELVYET 61 VRVPGCAHHA DSLYTYPVAT QCHCGKCDSD STDCTVRGLG PSYCSFGEMK
Molecular weight (Da) (Approximately 40% of the total molecular weight of the molecule is due to glycosylation)	15,200	18,500

The amino acid sequences of the two FSH subunits are identical to the endogenous human FSH sequences. The expressing cell line can influence the characteristics of the recombinant FSH. Differences in glycosylation profile, salic acid pattern and isoform profile have been documented between follitropin delta and recombinant FSH products, such as follitropin alpha and follitropin beta which are produced in Chinese hamster ovary (CHO) cell lines.

Compared to unglycosylated FSH, the glycosylated FSH contains:

- both α2,3- and α2,6-linked sialic acid (2,6-linked sialic acid is absent in CHO-derived recombinant FSH) and higher overall sialic acid content than CHO-derived recombinant FSH;
- different sugars such as *N*-acetylgalactosamine;
- additional linkages between carbohydrates such as bisecting *N*-acetylglucosamine and antennary fucose; and
- a higher proportion of tetra-antennary structures.

Pre-meeting public submissions

Two public submissions were received and both supported the proposal. The main points were that the entry in Appendix D for UROFOLLITROPIN (human follicle stimulating hormone) for human use covers its recombinant forms as well. However, for clarity it would be desirable to add follitropin delta to Appendix D.

Summary of ACMS advice to the delegate

The Committee advised that follitropin delta should be entered in Schedule 4 with an Appendix D, Item 1 listing.

The recommended wording for the follitropin delta entry is as follows:

Schedule 4 –New Entry

#FOLLITROPIN DELTA.

Appendix D –New Entry

Item 1. Poisons available only from or on the prescription or order of an authorised medical practitioner.

FOLLITROPIN DELTA (recombinant human follicle-stimulating hormone) for human use.

The Committee recommended an implementation date of **1 June 2017.**

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (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.

The reasons for the advice comprised the following:

- The benefit of follitropin delta is that an additional medicine can be used in assisted reproductive technology (ART).
- The risks around follitropin delta should be mitigated, provided that it is prescribed by an appropriate specialist skilled in the area of ART risks, such as ovarian hyper-stimulation syndrome (OHSS).
- Pharmacologically, follitropin delta appears to be similar to follitropin alpha and follitropin beta, with minor pharmacokinetic differences. The use and toxicity of follitropin delta are similar to follitropin alpha and follitropin beta. Toxicity is able to be managed by appropriate specialists.
- Follitropin delta is only to be used in ART and only after endocrine function testing. Therefore, it should only be prescribed by medical specialists skilled in this area (i.e., O&G specialists). Dosage is clearly related to the required endocrine functioning, which is to be completed before use, and body weight of the patient. Product information will include the requirements for dosing according to endocrine testing.
- Follitropin alpha and beta are already scheduled in Appendix D, Item 1. It is appropriate for consistency that follitropin delta be scheduled in the same way.

Delegate's considerations

The delegate considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACMS advice
- Section 52E of the Therapeutic Goods Act 1989
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegate's interim decision

The delegate's interim decision is that a new Schedule 4 entry for follitropin delta with an Appendix D Item 1 listing is appropriate.

The proposed wording for the schedule and appendix entries is as follows:

Schedule 4 – New Entry

#FOLLITROPIN DELTA.

Appendix D, Item 1 – New Entry

FOLLITROPIN DELTA (recombinant human follicle-stimulating hormone) for human use.

Index

FOLLITROPIN DELTA
cross reference: FOLLICLE-STIMULATING HORMONE, RECOMBINANT HUMAN

Schedule 4
Appendix D, Item 1

The proposed implementation date is **1 June 2017**.

The delegate considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (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.

The reasons for the interim decision are the following:

- The delegate acknowledges the committee's advice.
- Follitropin delta is an additional medicine for assisted reproductive technology (ART).
- Follitropin delta appears to be similar to follitropin alpha and follitropin beta, with minor pharmacokinetic differences.
- Follitropin alpha and beta are already listed in Appendix D, item 1. For consistency it is appropriate that follitropin delta be similarly scheduled.

Public submissions on the interim decision

No public submissions were received in response to the interim decision for follitropin delta.

Delegate's final decision

The delegate has confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegate's final decision is to create new Schedule 4 and Appendix D entries for follitropin delta with an implementation date of **1 June 2017**.

Part B - Final decisions on matters not referred to an expert advisory committee

1. New Chemical Entities – medicines for human therapeutic use

Summary of delegate's final decisions

The implementation date of the below final decisions is **1 June 2017** unless separately specified.

Substance	Final Decision
Albutrepenonacog alfa	Albutrepenonacog alfa is exempt from scheduling as it falls under the Appendix A entry for human blood products.
Sebelipase alfa	**Schedule 4– New Entry** SEBELIPASE ALFA.
Meningococcal Group B Vaccine	**Schedule 4 – New Entry** MENINGOCOCCAL GROUP B VACCINE. **Index – New Entry** **MENINGOCOCCAL GROUP B VACCINE** cross reference: Neisseria Meningitidis Serogroup B Recombinant LP2086 (MnB rLP2086) Subfamily A Protein and Subfamily B Protein Schedule 4
Sodium Phenylbutyrate	**Schedule 4 – New Entry** SODIUM PHENYLBUTYRATE.
Silodosin	**Schedule 4 – New Entry** SILODOSIN.
Dengue Vaccine Also known as: Live attenuated chimeric dengue virus (serotypes 1, 2, 3 & 4)	**Schedule 4 – New Entry** DENGUE VACCINE. **Index – New Entry** **DENGUE VACCINE** crosses reference: LIVE ATTENUATED CHIMERIC DENGUE VIRUS (SEROTYPES 1, 2, 3 & 4) Schedule 4

1.1 Albutrepenonacog alfa

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of albutrepenonacog alfa, a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Albutrepenonacog alfa is a recombinant form of coagulation factor IX (FIX) genetically fused to human albumin to prolong clotting activity and is indicated for IV use in adults and children with haemophilia B to control and prevent bleeding episodes.

Nomenclature: Albutrepenonacog alfa (ABN and INN).

Scheduling status

Albutrepenonacog alfa is currently exempt from scheduling because it is captured under the Appendix A entry for HUMAN BLOOD PRODUCTS under item (c)(iv) clotting factors in the current Poisons Standard:

Appendix A – General exemptions

HUMAN BLOOD PRODUCTS including:

a) whole blood;

b) blood components including red cells, white cells, platelets and plasma (including cryoprecipitate); and

c) the following plasma-derived therapeutic proteins; and their equivalent recombinant alternatives:

i) albumin;

ii) anticoagulation complex;

iii) C1 esterase inhibitors;

iv) clotting factors;

v) fibrinogen;

vi) protein C;

vii) prothrombin complex concentrate (PCC) ; and

viii) thrombin.

International regulations

Albutrepenonacog alfa is classified as a Schedule D (biological) drug in Canada and is a prescription only medicine in the EU and the USA. Albutrepenonacog alfa is not classified in New Zealand.

Delegate's considerations

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report;
- The advice of the Advisory Committee on Prescription Medicines; and
- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Appendix A.

Delegate's final decision

The delegate has made a final decision that albutrepenonacog alfa is exempt from scheduling as it falls under the Appendix A entry for human blood products in the Poisons Standard.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (b) the purpose and the extent of use of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The reasons for the final decision comprise the following:

- Albutrepenonacog alfa is a recombinant form of a plasma-derived therapeutic clotting protein and is therefore captured by the Appendix A entry for human blood products.
- Albutrepenonacog alfa is an NCE with no marketing experience in Australia. Expected benefits are control of bleeding episodes in patients with haemophilia B, risks are as for other recombinant products in this class, including hypersensitivity.
- Albutrepenonacog alfa is used by a defined patient population under the supervision of a physician experienced in the treatment of haemophilia B. Monitoring is routine in management of the disorder.
- The potential for abuse of albutrepenonacog alfa is unlikely.

1.2 Sebelipase alfa

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of sebelipase alfa, a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Sebelipase alfa is an enzyme replacement therapy that addresses the underlying cause of lysosomal acid lipase deficiency (LAL-D) by reducing substrate accumulation in the lysosomes of cells throughout the body.

Sebelipase alfa is indicated for long-term enzyme replacement therapy (ERT) in patients of all ages with lysosomal acid lipase deficiency (LAL-D).

Australian Approved Name (AAN) and International Non-Proprietary Name (INN): Sebelipase alfa

Scheduling status

Sebelipase alfa is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Sebelipase alfa is not classified in New Zealand and Canada.

Sebelipase alfa is approved for use in the USA and the EU.

Delegate's consideration

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling (ACMS) was not consulted.

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report; and

- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include Sebelipase alfa in Schedule 4, with an implementation date of **1 June 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

SEBELIPASE ALFA.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (b) the purpose and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse.

The delegate decided that the reasons for the final decision comprise the following:

- It is an NCE with no clinical experience in Australia apart from clinical trials.
- The risks and benefits of Sebelipase alfa have been considered and are outlined in the Product Information (PI), and the TGA evaluation reports.
- Sebelipase alfa is indicated for long-term enzyme replacement therapy in patients with lysosomal acid lipase deficiency.
- It has no previous experience of use in Australia outside the clinical trial setting but has recently been approved overseas.
- Sebelipase alfa is a recombinant human lysosomal acid lipase given by intravenous infusion. Its use requires medical intervention, evaluation and monitoring by a medical practitioner.
- Labelling needs to comply with the requirements for an injectable prescription only medicine.
- It does not appear to produce dependency and the abuse potential appears low.

1.3 Meningococcal Group B Vaccine

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of Neisseria Meningitidis Serogroup B Recombinant LP2086 (MnB rLP2086) Subfamily A Protein and Subfamily B Protein (Meningococcal Group B Vaccine), a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Meningococcal Group B Vaccine consists of two recombinant lipidated factor H binding protein (fHBP) variants from N. meningitidis serogroup B. fHBP.

Meningococcal Group B Vaccine is indicated for individuals 10 years and older for active immunisation to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroup B.

ABN – Neisseria Meningitidis Serogroup B Recombinant LP2086 (MnB rLP2086) Subfamily A Protein and Subfamily B Protein (Meningococcal Group B Vaccine)

Scheduling status

Meningococcal Group B Vaccine is not specifically scheduled in the current Poisons Standard but is captured under the following group entry:

Schedule 4

MENINGOCOCCAL VACCINE.

International regulations

Meningococcal Group B Vaccine is not specifically classified in New Zealand. However, it would be classified under the group entry, MENINGOCOCCAL VACCINE, as a prescription medicine except when administered to a person 16 years of age or over by a registered pharmacist who has successfully completed a vaccinator training course approved by the Ministry of Health and who is complying with the immunisation standards of the Ministry of Health.

Delegate's consideration

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report; and
- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include Meningococcal Group B Vaccine in Schedule 4, with an implementation date of **1 June 2017**.

The delegate has decided that the wording for the schedule and index entries will be as follows:

Schedule 4 – New Entry

MENINGOCOCCAL GROUP B VACCINE.

Index – New Entry

MENINGOCOCCAL GROUP B VACCINE
cross reference: Neisseria Meningitidis Serogroup B Recombinant LP2086 (MnB rLP2086) Subfamily A Protein and Subfamily B Protein

Schedule 4

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* is: (a) the risks and benefits of the use of a substance.

The delegate decided that the reasons for the final decision comprise the following:

- Meningococcal Group B Vaccine is an NCE with no clinical and marketing experience in Australia;
- The proposed indication is for individuals 10 years and older for active immunisation to prevent invasive meningococcal disease caused by Neisseria meningitidis serogroup B; and
- The potential for abuse of Meningococcal Group B Vaccine is unlikely.

1.4 Sodium phenylbutyrate

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of sodium phenylbutyrate, a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Sodium phenylbutyrate is a pro-drug and is rapidly metabolised to phenylacetate. Phenylacetate is a metabolically active compound that conjugates with glutamine via acetylation to form phenylacetylglutamine which is then excreted by the kidneys.

Sodium phenylbutyrate is indicated as adjunctive therapy in the chronic management of urea cycle disorders and should be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, and protein-free calorie supplements). Sodium phenylbutyrate is indicated in all patients with neonatal-onset presentation (complete enzyme deficiencies, presenting within the first 28 days of life). It is also indicated in patients with late-onset disease (partial enzyme deficiencies, presenting after the first month of life) who have a history of hyperammonaemic encephalopathy. Sodium phenylbutyrate has not been studied in the geriatric (> 65 years of age) population.

Australian Approved Name (AAN) and International Non-Proprietary Name (INN): Sodium phenylbutyrate.

Scheduling status

Sodium phenylbutyrate is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Sodium phenylbutyrate is classified as a prescription medicine in New Zealand, Canada and USA.

Delegate's consideration

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report; and
- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include Sodium phenylbutyrate in Schedule 4, with an implementation date of **1 June 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

SODIUM PHENYLBUTYRATE.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (b) the purpose and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse.

The delegate decided that the reasons for the final decision comprise the following:

- Sodium phenylbutyrate is an NCE with no marketing experience in Australia.
- The risks and benefits of Sodium phenylbutyrate have been considered and are outlined in the Product Information (PI) and the TGA evaluation reports.
- Sodium phenylbutyrate has been used for more than a decade internationally but there is no marketing experience in Australia.
- Sodium phenylbutyrate has risks that require medical intervention, evaluation and monitoring by the medical practitioner.
- Treatment should only be initiated and monitored by a health professional experienced in the treatment of urea cycle disorders.
- It does not appear to produce dependency and the abuse potential appears low

1.5 Silodosin

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of silodosin, a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Silodosin is an alpha-adrenergic blocker that blocks alpha1A adrenoreceptors in the prostate gland, bladder, urethra and blood vessels. When these receptors are activated, they cause the muscles controlling the flow of urine to contract. By blocking these receptors, silodosin allows these muscles to relax, making it easier to pass urine and relieving the symptoms of benign prostatic hyperplasia (BPH).

Silodosin is indicated for the relief of lower urinary tract (LUTS) associated with BPH in adult men.

Australian Approved Name (AAN) and International Non-Proprietary Name (INN): Silodosin

Scheduling status

Silodosin is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Silodosin is not classified in New Zealand.

Silodosin is a prescription only medicine in Canada, the USA and EU.

Delegate's consideration

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report; and

- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include silodosin in Schedule 4, with an implementation date of **1 June 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

SILODOSIN.

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; (b) the purpose and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (e) the potential for abuse.

The delegate decided that the reasons for the final decision comprise the following:

- Silodosin is an NCE with no clinical experience in Australia.
- The risks and benefits of Silodosin have been considered and are outlined in the Product Information, Delegate's Request for ACM advice and the TGA evaluation reports
- Silodosin has no previous experience of use in Australia but has been available for several years internationally.
- Silodosin is proposed for use in the hospital and community. However the majority of use will be in the community.
- Treatment should be initiated by a medical practitioner. Silodosin has risks that require medical intervention, evaluation and monitoring by a medical practitioner.
- Labelling needs to comply with the requirements for a prescription only medicine.
- It does not appear to produce dependency and the abuse potential appears to be low.

1.6 Dengue Vaccine (Live attenuated chimeric dengue virus (serotypes 1, 2, 3 & 4))

Scheduling proposal

The delegate considered an application from the Therapeutic Goods Administration (TGA) for the scheduling of live attenuated chimeric dengue virus (serotypes 1, 2, 3 & 4) (Dengue Vaccine), a new chemical entity (NCE) for a human therapeutic medicine.

Substance summary

Live attenuated chimeric dengue virus (serotypes 1, 2, 3 & 4) is a live attenuated tetravalent vaccine, composed of four live recombinant, attenuated vaccines (CYD-1–4) based on a well-characterized Yellow Fever virus strain 17D (YFV 17D) genomic backbone modified to express the pre-membrane and envelope genes of one of the four Dengue virus serotypes.

Live attenuated chimeric dengue virus (serotypes 1, 2, 3 & 4) is indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 60 years of age living in endemic areas.

Scheduling status

The Dengue vaccine (live attenuated chimeric dengue virus (serotypes 1, 2, 3 & 4) is not specifically scheduled and is not captured by any entry in the current Poisons Standard.

International regulations

Live attenuated chimeric dengue virus (serotypes 1, 2, 3 & 4) (Dengue vaccine) is not classified in New Zealand.

Delegate's consideration

The delegate decided to make a delegate-only decision. The Advisory Committee on Medicines Scheduling was not consulted.

The delegate considered the following in regards to this application for scheduling:

- Subsection 52E(1) of the *Therapeutic Goods Act 1989*;
- The Scheduling Policy Framework (2015) scheduling factors;
- The TGA evaluation report;
- The new drug application.

The delegate noted that currently there are no issues of concern that require additional control other than by inclusion in Schedule 4.

Delegate's final decision

The delegate has made a final decision to amend the Poisons Standard to include live attenuated chimeric dengue virus (serotypes 1, 2, 3 & 4) (Dengue Vaccine) in Schedule 4, with an implementation date of **1 June 2017**.

The delegate has decided that the wording for the schedule entry will be as follows:

Schedule 4 – New Entry

DENGUE VACCINE.

Index – New Entry

DENGUE VACCINE
crosses reference: LIVE ATTENUATED CHIMERIC DENGUE VIRUS (SEROTYPES 1, 2, 3 & 4)

Schedule 4

The delegate decided that the relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989* are: (a) the risks and benefits of the use of a substance; and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The delegate decided that the reasons for the final decision comprise the following:

- It is an NCE with no marketing experience in Australia;
- The proposed indication for the CYD dengue vaccine is for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 60 years of age living in endemic areas. Living in endemic areas would require medical assessment;
- The approved dose is as a suspension for injection; and
- The potential for abuse of live attenuated chimeric dengue virus (serotypes 1, 2, 3 & 4) is unlikely.